

The Risk of Malignancy Associated With Psoriasis

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Objective: To measure the incidence of cancer in patients with psoriasis, stratified by the severity of their disease.

Design: A cohort study.

Setting: Administrative claims records obtained from Medicaid programs in 3 US states.

Participants: All individuals in the claims database who qualified for 1 of the 5 following groups: severe psoriasis as defined by treatment with systemic medication, less severe psoriasis, severe eczema, history of organ transplantation, and hypertension.

Main Outcome Measure: A diagnosis of cancer.

Results: Individuals with severe psoriasis were more likely to develop a malignancy than those with hypertension (risk ratio, 1.78; 95% confidence interval [CI],

1.32-2.40). The risk of malignancy in the severe psoriasis group approaches that in patients with organ transplants (risk ratio, 2.12; 95% CI, 1.80-2.50). Most of these cancers were nonmelanoma skin cancers and lymphoproliferative malignancies. Those with less severe psoriasis were only slightly more likely to develop a new malignancy than those with hypertension (risk ratio, 1.13; 95% CI, 1.03-1.25).

Conclusions: Patients with psoriasis are at an increased risk of developing a malignancy compared with patients with hypertension. The increased risk is greatest for those with severe disease (ie, patients with psoriasis treated with systemic agents) and minimal (if an increased risk at all) for those with less severe disease compared with those in the hypertension group. The increased risk is mainly for lymphoproliferative cancers and nonmelanoma skin cancers.

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PSORIASIS AFFECTS about 1% to 2% of the US population and varies in severity, clinical type, and response to therapy.^{1,2} First clinical presentation most commonly occurs in young adulthood, and psoriasis could last a lifetime.^{1,2} Although psoriasis has seldom been linked directly to mortality, it can cause severe morbidity and psychological distress.¹ Most patients with psoriasis are treated with topical agents, which are believed to have few systemic adverse effects. However, patients with severe disease are often treated with potent systemic agents, some of which have been associated with increasing an individual's risk of developing a malignancy.¹⁻⁴ In fact, some previous studies have shown that patients with psoriasis have an increased risk of developing a malignancy.⁵⁻¹² However, these studies primarily investigated hospitalized individuals with psoriasis or those who had received psoralen with

UV-A light treatment (PUVA), which has been well proven to increase the risk of malignancy.¹¹⁻¹⁴

Because malignancy in the general population is relatively rare and most patients with psoriasis are treated as outpatients, it can be very difficult to accurately measure the risk of malignancy in patients with psoriasis. Therefore, the goal of our study was to measure the incidence of cancer in patients with psoriasis, stratified by the severity of their disease.

RESULTS

We evaluated 259808 individuals. Owning to the large size of our database, we were able to observe 1101 individuals with severe psoriasis and 16519 individuals with less severe psoriasis for an average of more than 2 years (**Table 1**). About 6.2% of the patients in our Medicaid database who had psoriasis were classified in the se-

METHODS

POPULATION AND PERSON-TIME

Using a large US administrative database we designed a retrospective cohort study. Our database included data on participants in the Medicaid programs of 3 large states from July 1992 to March 1996. One state was located in the mid-Atlantic region, 1 in the midwestern region, and 1 in the southern region of the United States. Compared with the general population, Medicaid participants are more likely to be women, ethnic minorities, and children.¹⁵ All individuals included in our analytic data set were 20 years or older and had *International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM)* diagnostic code(s) consistent with a disease study group.

STUDY GROUPS

Individuals were classified into 1 of 5 study groups based on *ICD-9-CM* codes from medical claims and, when appropriate, National Drug Codes for specific medications used to treat these illnesses. Study groups were made up of individuals with (1) severe psoriasis as defined by a diagnosis of psoriasis and treatment with 1 or more systemic therapeutic agents (ie, psoralen, methotrexate, cyclosporin, etretinate, 6-thioguanine, hydroxyurea, tacrolimus, azathioprine, or acitretin); (2) less severe psoriasis as defined by a diagnosis of psoriasis and no treatment with any systemic agent; (3) severe eczema as defined by a diagnosis of eczema on at least 4 occasions in a 12-month period; (4) heart, kidney, or liver transplants and treatment with immunosuppressive agents; and (5) essential hypertension. When patients qualified for both the psoriasis group and another group, they were only classified as having psoriasis. The hypertension group was selected as our reference group because the cancer risk among hypertensive individuals is not expected to be substantially different from the risk in the general population. A true comparison group without disease was not studied because (1) surveillance for cancer may be less in those who do not regularly see a physician and (2) in Medicaid databases there is difficulty distinguishing whether the absence of claims indicates absence of disease or loss of eligibility.¹⁵ We estimated the risk of malignancy in patients with severe eczema to ensure that at least 1 of our comparison groups had as frequent skin examinations as those with severe psoriasis. Finally, we selected the organ transplant group to try to estimate the risk of malignancy associated with the use of immunosuppressive agents. Disease codes and drug codes are available from the corresponding author (D.J.M.) on request.

DEFINITION OF OUTCOME

The primary outcome of our study was the first occurrence of a claim that included a diagnosis of any cancer. This diagnosis must have occurred at least 6 months after the patient was classified into their study group. A cancer-free window was selected because we believe that previously diagnosed cancers would most likely be recorded within the first 6 months of available claims.

Cancer diagnoses were also based on *ICD-9-CM* codes. We qualitatively reviewed the full administrative records of a sample of patients with cancer codes to confirm that these individuals received care consistent with their cancer diagnosis (eg, a patient with lymphoma codes had multiple office visits and received appropriate therapy). Finally, in a subanalysis we altered the outcome definition such that all patients with a malignancy must have had at least 2 claims for the malignancy on different days within a 60-day window. These risk ratios were identical to those reported in the "Results" section (data not shown).

In addition we examined a priori 2 broad classes of malignancy: lymphoproliferative malignancies and non-melanoma skin cancers. Only for the analysis of nonmelanoma skin cancers were the *ICD-9-CM* codes for skin neoplasm of uncertain behavior included as part of the outcome definition because these cancers might have been treated before a definitive histologic diagnosis was made.

ANALYSIS

For each study group, incidence density for the onset of any malignancy was calculated with exact 95% Poisson confidence intervals (CIs). An incidence density is a measure of disease incidence that is corrected for unequal person-time. Incidence density was calculated by dividing the number of cancer cases (eg, malignancy in an individual with psoriasis) by the total person-time of follow-up (ie, person-years) of the study group. To calculate person-time, once a patient was classified into a study group we defined the starting point as the patient's first medical claim and the stopping point as the patient's last medical or pharmacy claim or the diagnosis of a malignancy.

Poisson regression was used to estimate unadjusted incidence density ratios and 95% CIs for the development of malignancy by comparing each study group with the hypertension group. Incidence density ratio is interpreted similarly to relative risk but takes into account unequal follow-up time. Finally, multivariate Poisson regression was used to adjust the rates for potential confounding by age, sex, and state of residence as well as to test for state by diagnosis effect modification.¹⁶ All statistical analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC).

vere group. Most of the individuals with severe psoriasis had received either methotrexate or etretinate therapy (**Table 2**). It should be noted that 17.7% of the individuals with severe psoriasis received therapy with more than 1 of these medications during the follow-up period. In contrast, 1.5% of the patients with severe eczema received therapy with 1 or more of the severe psoriasis medications. For all subjects combined, the malignancy rate ratio (RR) was somewhat greater in the

mid-Atlantic state compared with the other 2 states (1.19; 95% CI, 1.03-1.45), and increased with the age of the subject (eg, the risk ratio for the older-than-80-years age group was 4.09 [95% CI, 3.67-4.57] compared with the 20- to 29-year-old age group) (**Table 3**). The incidence density for the development of malignancy varied among our study groups, with those with severe eczema being the least likely to develop a malignancy and those with severe psoriasis being the most likely to develop a malignancy (Table 1).

Table 1. Study Population, Number of Malignancies, and the Incidence Density for a Malignancy*

Study Group	Persons, No.	Person-years	Average Follow-up, y	Malignancies, No.	Incidence Density, Person-year (95% CI)
Severe psoriasis	1101	2600	2.36	76	0.029 (0.023-0.036)
Less severe psoriasis	16519	37476	2.27	722	0.019 (0.018-0.021)
Severe eczema	3869	11050	2.86	165	0.015 (0.013-0.017)
Organ transplant	4015	9635	2.40	267	0.028 (0.024-0.031)
Hypertension	234304	569159	2.43	11780	0.021 (0.020-0.021)

*CI indicates confidence interval.

Table 2. Patients in the Severe Psoriasis Group Who Were Treated With Various Systemic Medications

Medication	Patients, No. (%)
Azathioprine	70 (6.4)
Cyclophosphamide	10 (0.9)
Cyclosporine	41 (3.7)
Etretinate, acitretin	436 (39.6)
Methotrexate	566 (51.4)
Methoxsalen	197 (17.9)
Tacrolimus	3 (0.3)
Hydroxyurea, 6-thioguanine	0

Table 4 gives the univariate and multivariate incidence ratios for malignancy with the hypertension groups as the reference group. Generally, the unadjusted and adjusted risk ratios varied by more than 15%, indicating that the univariate estimates were confounded by measured patient characteristics. Adjustment measures included state of residence, age in 10-year strata, and sex (Table 4). In our study, age and sex primarily caused confounding. Compared with the hypertension group (our reference group), individuals with severe psoriasis (those receiving therapy with systemic agents) and transplant patients were more likely to develop a malignancy (adjusted RR, 1.78 [95% CI, 1.32-2.40] and 2.12 [95% CI, 1.80-2.50], respectively). Individuals with less severe psoriasis may have had a slightly increased risk of developing cancer compared with our reference group (adjusted RR, 1.13; 95% CI, 1.03-1.25).

In addition, we looked in greater detail at 2 types of malignancies: lymphomas and nonmelanoma skin cancers. Generally, for all subjects lymphoma risk was greater in men than in women (RR, 1.59; 95% CI, 1.35-1.88) and was more common in the 60- to 69-year-old age group (RR, 1.50; 95% CI, 1.02-2.22) than in the 20- to 29-year-old age group. Skin cancer risk was greater in men than in women (RR, 1.39; 95% CI, 1.22-1.58) and also with increasing age. For example, the greatest risk was in the older-than-80-years age group (RR, 17.49; 95% CI, 10.41-29.38) compared with the 20- to 29-year-old age group. The risk of skin cancer was related to state of residence and was greatest in the southern state (RR, 2.11; 95% CI, 1.54-2.90) compared with the mid-Atlantic state.

The incidence RRs for both lymphoma and non-melanoma skin cancer were also greater in the 2 psoriasis groups than in the hypertension group and much greater in the severe psoriasis group than in the less se-

vere psoriasis group (**Table 5** and **Table 6**). The elevated risk ratio for the severe psoriasis group was similar to that for the organ transplant group. The elevated risk in the less severe psoriasis group was similar to that in the severe eczema group. Finally, most of the increased cancer risk for the severe psoriasis group and the less severe psoriasis group was because of the incidence of lymphoma or skin cancer among these groups (**Table 7**).

COMMENT

Using a large administrative database of US Medicaid enrollees, we demonstrated that individuals with psoriasis requiring treatment with systemic agents are almost twice as likely (after accounting for the effects of age and sex) to develop a malignancy than are individuals with hypertension. The magnitude of the increased risk in individuals with severe psoriasis is similar to that in patients with organ transplants. However, individuals with psoriasis who do not require treatment with systemic agents seem to have the same risk of malignancy as individuals with severe eczema, which may be equal to or slightly greater than our reference group (hypertension). We were not able to distinguish whether the increased risk in the severe group was due to drug treatments, the presence of severe psoriasis, or unmeasured risk factors for cancer that differ between individuals with severe psoriasis and hypertensive patients.

In our study we compared the risk of malignancy for individuals with psoriasis of varying severity, severe eczema, and organ transplants with the risk in individuals with hypertension. We did this to compare the rates of malignancy in our study groups with a group of individuals from the same population (ie, all individuals in our study are part of the US Medicaid population) and specifically avoid ascertainment bias and control at least partially for socioeconomic status. We believe that the hypertension group is likely to reflect the true population rate of developing a malignancy in our Medicaid population. An alternative reference group would have been data from the Surveillance, Epidemiology and End Results (SEER) program. However, we believe that a control group made up of Medicaid recipients is more appropriate because socioeconomic factors and other social factors are related to the risk of malignancy and would differ between SEER data and Medicaid enrollees. In our study there is no reason to expect that these sociodemographic factors differ between those with hypertension and those with psoriasis. In addition, we estimated the

Table 3. Rate (95% Poisson Confidence Interval) of Malignancy per Person-year Stratified by Sex and 10-Year Age Groups

Age, y	Men/Women		
	Less Severe Psoriasis	Severe Psoriasis	Hypertension
20-29	0.009 (0.005-0.016)/0.006 (0.004-0.009)	0.021 (0.002-0.075)/0.016 (0.003-0.046)	0.005 (0.003-0.007)/0.005 (0.004-0.006)
30-39	0.011 (0.007-0.015)/0.011 (0.008-0.015)	0.019 (0.006-0.045)/0.020 (0.007-0.043)	0.007 (0.006-0.008)/0.008 (0.007-0.009)
40-49	0.019 (0.014-0.024)/0.020 (0.015-0.025)	0.045 (0.022-0.080)/0.017 (0.006-0.036)	0.011 (0.010-0.012)/0.0153 (0.014-0.016)
50-59	0.027 (0.021-0.035)/0.019 (0.015-0.024)	0.060 (0.030-0.108)/0.022 (0.010-0.044)	0.019 (0.018-0.021)/0.022 (0.021-0.023)
60-69	0.037 (0.029-0.047)/0.024 (0.019-0.030)	0.037 (0.102-0.087)/0.041 (0.019-0.077)	0.027 (0.025-0.029)/0.027 (0.026-0.028)
70-79	0.032 (0.022-0.044)/0.035 (0.027-0.044)	0.084 (0.017-0.243)/0.036 (0.010-0.091)	0.035 (0.032-0.038)/0.029 (0.027-0.030)
≥80	0.029 (0.016-0.050)/0.035 (0.026-0.056)	0.056 (0.001-0.310)/0.056 (0.007-0.200)	0.041 (0.036-0.046)/0.031 (0.002-0.004)

Table 4. Relative Rate Ratio (95% Confidence Interval) for All Malignancies*

Diagnostic Group	Unadjusted Rate Ratio	Adjusted Rate Ratio
Hypertension	1.00 (Reference)	1.00 (Reference)
Severe psoriasis	1.42 (1.12-1.80)	1.78 (1.32-2.40)
Less severe psoriasis	0.93 (0.86-1.10)	1.13 (1.03-1.25)
Severe eczema	0.83 (0.72-0.95)	1.04 (0.85-1.28)
Organ transplant (heart, liver, or kidney)	1.35 (1.19-1.52)	2.12 (1.80-2.50)

*Poisson regression was used to adjust for age (as broken into 10-year intervals), the patient's state of origin, and sex.

Table 5. Relative Rate Ratio (95% Confidence Interval) for Lymphoproliferative Malignancies*

Diagnostic Group	Unadjusted Rate Ratio	Adjusted Rate Ratio
Hypertension	1.00 (Reference)	1.00 (Reference)
Severe psoriasis	7.80 (4.42-12.81)	7.95 (4.94-12.79)
Less severe psoriasis	2.18 (1.66-2.84)	2.11 (1.63-2.74)
Severe eczema	1.95 (1.15-3.12)	1.70 (0.99-2.95)
Organ transplant (heart, liver, or kidney)	3.12 (1.98-4.71)	3.35 (2.23-5.03)

*Poisson regression was used to adjust for age (broken into 10-year intervals), the patient's state of origin, and sex.

risk of developing a malignancy in patients with organ transplants to obtain a benchmark for rates that are likely to be associated with the use of immunosuppressive medications, many of which are used or might be used in the future to treat psoriasis. Finally, we estimated the risk of malignancy in patients with severe eczema to ensure that at least 1 of our comparison groups had frequent skin examinations and thereby had a similar opportunity to have skin cancers diagnosed as those with psoriasis. There is no known disease-related reason that patients with severe eczema should be inherently at higher risk than those with hypertension for developing skin cancer. However, a few patients (1.1%) in the severe eczema group received either therapies similar to those in our severe psoriasis group or UV light therapy that has been advocated for the treatment of eczema and might increase skin cancer risk.

Previous studies have evaluated the risk of patients with psoriasis for developing a malignancy. This topic has been of interest for several reasons but especially because psoriasis is a life-long disease and several of the therapies used to treat it (such as those that we used to define disease severity) are potentially carcinogenic.⁵⁻⁸ Many of the studies that evaluated the risk of malignancy in individuals with psoriasis compared the individuals with psoriasis who required hospitalization with population-based cancer registries and demonstrated that individuals with psoriasis are at an increased risk of developing a malignancy compared with the population at large.¹⁰

For example, a recent study by Hannuksela-Svahn et al⁹ using the Finnish Hospital Discharge Register and the Finnish Cancer Registry demonstrated that individu-

als with psoriasis were about 30% more likely to develop a malignancy than others in the Finnish population. They also demonstrated that many of these malignancies were skin cancers and lymphomas. However, to be considered as having psoriasis in their study, the patient must have been discharged from the hospital with a diagnosis of psoriasis. No information is available in their study on individuals with less severe psoriasis. In a study from Denmark that found similar results, the authors estimated that while 2% to 3% of the entire population has psoriasis, only 4% of those individuals required hospitalization.¹⁷

Finally, several reports have been published using data from the PUVA Follow-up Study that has shown that individuals with psoriasis who have had long-term exposure to PUVA are at an increased risk of developing a malignancy.¹¹⁻¹⁴ These longitudinal series of studies concentrate on a cohort of patients who received PUVA therapy in multiple centers across the United States in 1985. Again, no information is available on individuals with less severe psoriasis. In addition, rates of malignancies in the PUVA group are often compared with US population rates. This comparison may potentially be biased by factors such as the socioeconomic factors for receiving Medicaid.

There are several potential limitations to our study. Primarily because of the time frame studied, very few individuals with psoriasis received treatment with cyclosporine, which was not approved by the Food and Drug Administration for the treatment of severe psoriasis until 1997. This is especially important because there is a general concern that patients being treated with this medication may be at risk for developing a malignancy.^{2,4,18-20}

Table 6. Relative Rate Ratio (95% Confidence Interval) for Nonmelanoma Skin Malignancies and Skin Lesions That Were Coded Malignancy of Unknown Behavior*

Diagnostic Group	Unadjusted Rate Ratio	Adjusted Rate Ratio
Hypertension	1.00 (Reference)	1.00 (Reference)
Severe psoriasis	3.19 (2.04-4.77)	4.15 (2.52-6.84)
Less severe psoriasis	1.86 (1.61-2.16)	2.35 (1.96-2.82)
Severe eczema	1.57 (1.17-2.07)	2.14 (1.50-3.05)
Organ transplant (heart, liver, or kidney)	2.45 (1.90-3.12)	4.36 (2.89-5.25)

*Poisson regression was used to adjust for age (as broken into 10-year intervals), the patient's state of origin, and sex.

Our study cannot differentiate between the 2 most obvious causes for the increased risk of cancer in the severe psoriasis group, namely, the severity of psoriasis necessitating treatment with systemic agents or the use of systemic agents alone. In addition, we could not determine how long an individual needs to be exposed to a systemic agent before their risk increases. Although the average observation period for an individual with psoriasis in our study was about 2 years, many of these individuals probably had been receiving therapy with these agents previously.

Although our study was very large, we did not have sufficient statistical power to determine if one agent is more likely to increase the risk of cancer than another agent. However, with the recent advent of sequential or rotational therapy (the practice of using an agent for short periods and then rotating to a second agent), differentiating cancer risk for a single agent may be even more difficult.²¹ There were undoubtedly some patients classified as having less severe psoriasis who, prior to our study time window, might have had severe psoriasis. The error was probably small, but it could have led us to overestimate the risk of malignancy in both the severe group and the less severe group. Finally, while we required a person to have a disease of interest for at least 6 months prior to the diagnosis of cancer, it is still possible that a cancer diagnosis was not incident to the onset or treatment of psoriasis (eg, the cancer diagnosis might have predated the psoriasis diagnosis). A recent study that validated a coding scheme for determining if a patient had breast cancer in the US Medicare system noted that some of the cases that were thought to be incident were actually cases of recurrent disease.²² However, there is no reason to believe that the error in diagnosing a prior malignancy should be different in our main comparison group (hypertension) and psoriasis group. Therefore, the potential bias would be nondifferential and at worst might result in our underestimating the true increased risk in the severe psoriasis group.

One critical limitation to our study and any administrative database study is estimating the validity of the ICD-9-CM coding schemes to determine study groups and patient outcomes. We did qualitatively demonstrate that subjects in our study groups and subjects with cancer diagnoses received care consistent with their ICD-

Table 7. Relative Rate Ratio (95% Confidence Interval) for Malignancies, Excluding Nonmelanoma Skin Malignancies and Lymphoproliferative Malignancies*

Diagnostic Group	Univariate Rate Ratio	Multivariate Rate Ratio
Hypertension	1.00 (Reference)	1.00 (Reference)
Severe psoriasis	1.17 (0.47-2.94)	1.46 (1.04-2.05)
Less severe psoriasis	0.82 (0.61-1.11)	1.00 (0.90-1.12)
Severe eczema	0.62 (0.34-1.15)	0.91 (0.73-1.15)
Organ transplant (heart, liver, or kidney)	1.20 (0.74-1.94)	1.89 (1.58-2.26)

*Poisson regression was used to adjust for age (as broken into 10-year intervals), the patient's state of origin, and sex.

9-CM codes (eg, a patient with lymphoma received appropriate chemotherapy). We also repeated our analysis, requiring at least 2 different claims for the same malignancy at least 60 days apart. Using our coding scheme, it would be much less likely that the outcome was due to a coding error. The results of our analyses were the same. However, the gold standard is to verify ICD-9-CM coding schemes by reviewing patient charts. Because of concerns surrounding patient confidentiality in the Medicaid benefits system, we were not able to verify that an individual had severe psoriasis when placed in our severe psoriasis group or truly ascertain that a patient with a code for lymphoma truly had lymphoma. We could only adjust our findings for variables coded in the databases. It is possible that the effect estimates could change if these unmeasured confounders (such as cigarette use, alcohol use, occupational exposures, etc) were measured.

In summary, our study adds to the growing body of literature showing that patients with severe psoriasis are at an increased risk of developing a malignancy, especially nonmelanoma skin cancers and lymphoma in our study. As has been frequently addressed concerning the use of PUVA, the potential risk of developing cancer must be weighed against the benefit of the therapy.^{7,23,24} We do not know if the risk of malignancy will diminish with the advent of rotational use of systemic agents. However, it should be noted that about 17% of our patients with severe psoriasis received more than 1 systemic agent. Finally, because our database included patients seen on an outpatient basis, we were able to estimate the risk of malignancy in patients with less severe psoriasis. This group may be at a slight overall increased risk of developing a malignancy compared with individuals with hypertension, specifically for developing nonmelanoma cancers of the skin and lymphoma. The risk is similar to the risk seen in patients with severe eczema.

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