

Evaluation of cancer risk related to atopic dermatitis and use of topical calcineurin inhibitors

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Summary

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Conflicts of interest

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Cases of lymphoma or cutaneous cancer have been observed following use of topical calcineurin inhibitors (TCIs), but it is unclear whether TCI use increases cancer risk. We used published literature to assess the extent to which atopic dermatitis (AD) or TCI use is associated with lymphoma, melanoma, basal cell carcinoma and squamous cell carcinoma. We searched the literature and summarized the results of all studies that provided data on the absolute or relative frequency of any malignancy among patients with AD or eczema or among patients using TCIs. The relative risk for all lymphoma in broad populations of AD or eczema ranged from 0.7 to 1.8. Available data on lymphoma following TCI use were inconsistent and insufficient to draw a conclusion about the causal role of TCIs. We found no evidence indicating that melanoma or nonmelanoma skin cancer is associated with TCI use. A bias analysis showed that cutaneous T-cell lymphomas initially misdiagnosed and treated as AD would lead to overestimation of the association between TCI use and lymphoma. However, there are only sparse data on specific malignancies among TCI-treated patients. The short duration of typical TCI exposure hinders conclusions about longer exposure. There is insufficient evidence in the epidemiological literature to infer whether TCIs do or do not cause malignancy.

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Atopic dermatitis (AD) is a common inflammatory skin disease that has a chronic, relapsing course.^{1–3} AD treatment predominantly involves frequent use of emollients and topical steroids. In the U.S.A., topical pimecrolimus was approved in December 2001 for short-term or intermittent treatment of mild or moderate AD, and topical tacrolimus was approved in December 2000 for short-term and noncontinuous treatment of moderate to severe AD.

In early 2006, the U.S. Food and Drug Administration announced that the long-term safety of using topical calcineurin inhibitors (TCIs) (pimecrolimus and tacrolimus) for AD had not been established. The announcement, accompanied by a 'black box' warning, indicated a potentially elevated risk of cancer, particularly skin cancer and lymphoma, associated with these medications and suggested that their use should be reserved for second-line treatment.⁴ The concern about risk of

skin cancer or lymphoma stemmed from case reports and animal data. Long-term safety data in humans were not available.^{5–7}

Case reports are difficult to interpret as they provide no measure of absolute or comparative risk, and ascertainment of the cases typically incorporates selection bias. Therefore, we reviewed the published literature to describe the extent to which (i) AD is associated with lymphoma, melanoma, basal cell carcinoma and squamous cell carcinoma and (ii) TCI use among patients with AD is associated with these cancers or with total malignancies. Rather than posing screening criteria for inclusion or exclusion of studies, or listing strengths and weaknesses of studies with varying merit, we used the more direct and comprehensive method proposed by Maclure⁸ of 'deductive meta-analysis'. This approach calls for developing a list of hypotheses, either causal or referring to biases that could either underesti-

mate or overestimate the risk for cancer associated with AD or TCI use. The causal hypotheses we considered asserted that either AD or TCI use causes any of the following malignancies: cutaneous T-cell lymphoma (CTCL), basal cell carcinoma, squamous cell carcinoma, melanoma, and noncutaneous lymphomas. Noncausal hypotheses related to study design issues or other factors, such as diagnostic surveillance bias, that can distort the association between cancer and AD or TCI use. With this approach, published data are used to assess the tenability of the causal and noncausal hypotheses regarding the cancer associations (Table S1; see Supporting Information).

Materials and methods

A professional librarian searched Medline in January and again in December 2009 and EMBASE and the Cochrane Library in April 2010, to identify all studies that quantified the frequency of any malignancy among patients with AD or eczema or patients who were using TCIs (search terms used are provided in Data S1; see Supporting Information). We also checked cited references, but did not attempt to locate unpublished or nonrefereed data. Inclusion criteria were (i) case-control, cohort study or trial; (ii) internal comparator or population-based reference group; and (iii) reported absolute or relative risk [or odds ratio (OR)] for AD or eczema with TCI and any lymphoma or skin cancer. Although only two studies applied formal diagnostic criteria for identifying patients with AD (such as those proposed by Hanifin and Rajka⁹ or the U.K. working party definition¹⁰), we use the term AD when patients were identified with diagnostic codes that included AD or when diagnostic criteria for AD were applied. We cast a wide net with respect to design type and study quality so that we could evaluate the effect of potential biases on the rate ratio (RR) estimates.

From each identified paper an epidemiologist (P.T.) abstracted the following relevant data: the research question; study design; study population; definitions (e.g. exposures and outcomes); methods for ascertainment of AD, TCI exposure and cancers; all measures of association and confidence limits; and our evaluations of potential biases. A second epidemiologist independently checked all abstracted data. Without knowledge of the study results, we developed a conceptual model of potential causes and biases influencing the relative risks for AD or TCI use and skin cancer or lymphoma. As is generally the case for deductive meta-analysis,⁸ because we aimed to explore a variety of inter-related questions, no simple set of criteria regarding study protocols or inclusion criteria could identify all the potentially relevant studies. Narrow inclusion criteria that limit papers to a single outcome definition and a single exposure definition, an approach typically applied for systematic literature review and conventional meta-analysis, would not have been feasible for our purpose, because we aimed to assess a set of related questions rather than aggregate findings to estimate a single association. The broad search criteria that we used allowed us to identify studies that would allow us to evaluate a variety of biases that could have affected the associations of interest.

Results

We reviewed 268 abstracts, read 27 papers, and identified 22 potentially relevant publications evaluating outcomes among TCI users or risk factors for lymphoma or skin cancers. We excluded one¹¹ that was subject to immortal-time bias;¹² three others did not include internal or population-based comparator groups.^{13–15} One newly published article came to our attention after drafting this paper, but no other article was found in the updated search.

Skin lymphomas

No publication reported the relative risk for AD or eczema and skin lymphomas. Schneeweiss *et al.*¹⁶ reported an RR for cutaneous lymphomas and tacrolimus of 2.5 [95% confidence interval (CI) 0.5–12.6] and for pimecrolimus of 1.5 (95% CI 0.4–6.2) (Table 1^{16–18}). They reported progressive increases in incidence with increasing pimecrolimus use compared with low use of topical corticosteroids (TCS). These estimates had wide CIs because few cutaneous lymphoma cases had used TCIs. TCI use was based on insurance claims for pharmacy dispensings, which are not a perfect measure of actual use and may lead to underestimation of the association with cutaneous lymphoma.

Another study, conducted with electronic medical records of patients with a diagnosis of AD or eczema,¹⁸ showed that incident T-cell lymphomas, 80% of which were cutaneous, were more frequent among users of tacrolimus (RR 3.1; 95% CI 1.4–6.9) and pimecrolimus (RR 1.9; 95% CI 0.7–4.9). The investigators excluded four of 16 T-cell lymphoma cases for which CTCL was suspected at the time of TCI initiation, but nothing comparable was done for cases without TCI use. This imbalanced exclusion could underestimate the association between TCI use and T-cell lymphomas.

To assess whether TCI treatment of recalcitrant, undiagnosed yet symptomatic CTCL could explain the association between TCI use and skin lymphomas, we also evaluated the association between cutaneous lymphomas and another AD treatment, use of TCS. Two studies had relevant data. One case-control study nested within a U.K. general population cohort found a strong association between use of TCS and non-Hodgkin lymphoma with skin involvement.¹⁷ ORs for use of TCS > 30 days ranged from 15 to 83 (Table 1). A second study¹⁶ reported an RR of 2.5 (95% CI 1.0–6.7) for cutaneous lymphoma incidence with high-potency TCS compared with medium-potency TCS. Both studies are consistent with the 'reverse causation' hypothesis that early manifestations of undiagnosed lymphoma lead to treatment for a skin condition.

Noncutaneous lymphomas

Atopic dermatitis

Zhang *et al.*¹⁹ reported a weak association, albeit with wide CIs, between eczema and noncutaneous lymphomas (Table 2^{17,19–31}). They reported an OR for eczema and noncutaneous

Table 1 Studies that evaluated topical calcineurin inhibitors (TCIs) or topical corticosteroids (TCS) as risk factors for cutaneous lymphomas

Outcome, population and duration of TCI use	Rate ratio (95% CI) for TCIs	Rate ratio (95% CI) for TCS
Cutaneous lymphomas, broad population ¹⁶ (TAC: < 2 years use for 67% of exposed controls; PIM: < 2 years use for 71% of exposed controls)	TCS < 1 year: reference group PIM duration: < 1 year: 1.4 (0.3–6.2) 1–2 years: 1.8 (0.2–20.2) > 2 years: – TAC duration: not reported TCS ≤ 60 g: reference group PIM dispensed: ≤ 60 g: 0.9 (0.2–4.5) 61–100 g: 4.0 (0.2–68.3) > 100 g: – TAC dispensed: not reported Untreated dermatitis: reference TAC: 2.5 (0.5–12.6) PIM: 1.5 (0.4–6.2)	Potency of TCS Medium: reference group High: 2.5 (1.0–6.7)
Non-Hodgkin lymphoma with skin involvement in users of TCS or TCIs in a broad population ¹⁷ (Duration of TCI use not evaluable)	None reported	No TCS: reference group TCS duration of use: < 30 days: 3.8 (2.2–6.7) 1–6 months: 14.8 (8.3–26.6) 6 months–1 year: 25.8 (9.5–69.7) 1–2 years: 12.9 (4.0–41.9) > 2 years: 82.9 (9.3–740.2)
T-cell lymphoma ^a in patients with AD or eczema ¹⁸ (TAC: 2.4 years follow-up; PIM: 1.9 years follow-up)	No TCIs: reference group TAC 3.1 (1.4–6.9) PIM 1.9 (0.7–4.9)	

CI, confidence interval; TAC, tacrolimus; PIM, pimecrolimus; AD, atopic dermatitis. Publication not included: Ring *et al.*¹⁴ – no events; no comparator group, follow-up limited to 3 months. ^aOf T-cell lymphoma cases exposed to TCIs, 81% were documented through chart review to be cutaneous T-cell lymphoma; chart review was not performed for cases unexposed to TCIs.

B-cell non-Hodgkin lymphoma of 1.1 (95% CI 0.7–1.6); for diffuse large B-cell lymphoma, 1.3 (95% CI 0.7–2.3); and for marginal zone B-cell lymphoma, 1.1 (95% CI 0.3–3.9). Eczema was measured by patient self-report, a source of misclassification of AD. To assess the magnitude of possible bias from this misclassification, we used back-calculations with various values for sensitivity and specificity to detect AD^{32,33} and assumed these values were unrelated to lymphoma status. The calculations indicated that improved AD assessment would have had little effect.

We also considered the hypothesis that early itching of non-cutaneous lymphomas might be initially treated as symptoms of eczema and then followed by diagnosis of the lymphoma. This hypothesis predicts that short durations of AD or use of TCS, the latter a surrogate for AD, would be more strongly associated with diagnosis of noncutaneous lymphomas than long durations. Arellano *et al.*¹⁷ reported ORs for B-cell non-Hodgkin lymphoma of 1.2 (95% CI 0.8–1.7) for < 30 days of use of TCS, 1.6 (95% CI 1.1–2.3) for 30 days to 6 months of use of TCS, 1.9 for 6–12 months of use of TCS, and 1.2 for 12–24 months of use of TCS (see Table 3^{16–18,23}). ORs for Hodgkin lymphoma were 1.2 (95% CI 0.9–1.8) for < 30 days of use of TCS, 1.9 (95% CI 1.4–2.7) for 30 days to 6 months of use of TCS, 2.2 (95% CI 0.9–5.4) for 12–24 months of use of TCS, and 9.6 (95% CI 1.7–55.6) for > 24 months of use

of TCS. These observations are not consistent with symptomatic treatment of undiagnosed noncutaneous lymphoma.

Use of topical calcineurin inhibitors

Two studies reported on TCI use and noncutaneous lymphoma, both based on U.S. health insurance claims (Table 3). One study conducted in patients with insurance claims for AD²³ reported lower risk of nonmycosis fungoides or non-T-cell lymphoma after TCI use compared with nonuse, but with wide CIs. The other was a cohort study¹⁶ among all patients dispensed pimecrolimus or tacrolimus for the first time. Incidences of Hodgkin and non-Hodgkin lymphoma were elevated compared with a cohort of patients with untreated dermatitis matched by level of health care utilization. The result was a strong but nevertheless imprecise association between TCI use and Hodgkin lymphoma (tacrolimus RR 5.3; 95% CI 0.5–58.6; pimecrolimus RR 3.5; 95% CI 0.4–31), and a weaker association for TCI use and non-Hodgkin lymphoma (tacrolimus RR 1.4; 95% CI 0.5–4.0; pimecrolimus RR 1.6; 95% CI 0.8–3.5). This was the only study that showed a substantially elevated RR for TCI use and noncutaneous lymphomas. Although this result could also at least partially be explained by reverse causation from early treatment of Hodgkin lymphoma as nonspecific symptoms of itching coded

Table 2 Studies that evaluated atopic dermatitis (AD) or eczema as a risk factor for all lymphoma or specific lymphoma types, stratified by whether early follow-up was excluded

Outcome, population	Relative frequency in AD (95% CI)	AD exposure definition and ascertainment method
All lymphoma: after exclusion of early follow-up		
Lymphoproliferative malignancies after 6-month follow-up in a Medicaid population ²⁰	Severe eczema vs. hypertension: Crude: 2.0 (1.1–3.1) Adjusted: 1.7 (1.0–3.0) Lifetime: 0.8 (0.6–1.1)	Severe eczema: at least four eczema visits/claims in a 12-month period
Lymphoma in a broad population ²¹		Patient questionnaire asked about eczema during childhood, teenage years, adulthood and lifetime
Lymphoma in patients hospitalized for AD ²²	Follow-up 1–9 years: 3.3 (2.0–5.1) Follow-up ≥ 10 years: 1.1 (0.5–2.1)	Patients with an ICD code indicating a primary inpatient diagnosis of AD identified in the Swedish inpatient register
All lymphoma: no exclusion of early follow-up		
Lymphoma in a broad population ¹⁷	AD: 1.8 (1.4–2.4) Severe AD: 3.7 (1.4–9.9)	AD: history of diagnosis of AD (entered as READ code) Severe AD: referral to dermatologist AD not used to define index date
Lymphoma in an AD cohort ²³	Severe vs. nonsevere AD: 2.4 (1.5–3.8)	First claim for ICD code 691.8 (dermatitis other atopic) or 691 (dermatitis atopic) Severity of AD: Aged ≥ 3 years, at least four visits with AD claims in 1 year Aged 0–2 years, one visit to dermatologist Patient questionnaire used to assess physician-diagnosed medical history and date of condition
Lymphoma in a broad population ²⁴	OR 0.7 (0.5–1.0)	Kaiser medical record was abstracted for history of eczema; cases included only if > 5 years follow-up
Specific lymphomas: after exclusion of early follow-up		
Non-Hodgkin lymphoma in a broad population ²⁵	1.9 (0.6–5.8)	Self-report of eczema > 1 year prior to lymphoma diagnosis
Lymphoma types in a broad female population ¹⁹	Non-Hodgkin: 1.3 (0.9–1.9) B-cell non-Hodgkin: 1.1 (0.7–1.6) T-cell non-Hodgkin: 2.5 (1.1–5.7) Other non-Hodgkin: 2.0 (1.0–3.9) Follicular: 0.9 (0.4–1.7) Marginal zone B-cell: 1.1 (0.3–3.9) Diffuse large B-cell: 1.3 (0.7–2.3)	
Specific lymphomas: no exclusion of early follow-up		
Non-Hodgkin lymphoma in a broad population ²⁶	1.6 (1.1–2.4)	Medical history ascertained via interview, then checked via hospital records and general practitioner records
Non-Hodgkin lymphoma in a broad population ²⁷	0.5 (0.3–0.7)	All covariable information collected from cases in hospital and from controls at home or by telephone. Specifics of eczema ascertainment were not provided
Non-Hodgkin lymphoma in a broad population ²⁸	1.3 (0.6–2.6)	Eczema: combined childhood and allergic eczema; assessed from 1967 patient questionnaires; follow-up up to 31 years after exposure assessment
Non-Hodgkin lymphoma in a broad population ²⁹	1.2 (0.9–1.6)	Face-to-face interview to ascertain conditions diagnosed by a physician
Non-Hodgkin lymphoma in a broad population ³⁰	0.6 (0.4–1.0)	History assessed via nurse interview; no information on specifics for question regarding eczema/AD
Lymphoma types in a broad population ³¹	Diffuse large B-cell: 0.9 (0.4–1.8) Follicular: 2.3 (1.1–4.2) All non-Hodgkin: 1.2 (0.8–1.9)	Self-reported eczema and date of onset

CI, confidence interval; ICD, International Classification of Diseases; OR, odds ratio.

Table 3 Studies that evaluated use of topical calcineurin inhibitors (TCIs) or topical corticosteroids (TCS) as a risk factor for selected noncutaneous lymphomas or for all lymphoma

Outcome, population, duration of TCI use	Rate ratio (95% CI) for use of TCIs or TCS
Lymphoma excluding mycosis fungoides or T-cell lymphoma, in claims-based AD ²³ (TCI exposure duration not reported)	No TCI or TCS: reference group PIM: 0.6 (0.3–1.4) TAC: 0.7 (0.3–1.7) TCS high potency: 1.1 (0.70–1.7) TCS low potency: 1.0 (0.7–1.6)
Selected lymphomas in dermatitis ¹⁶ (TAC: < 2 years use for 67% of exposed controls; PIM: < 2 years use for 71% of exposed controls)	
Hodgkin lymphoma	Untreated dermatitis: reference group TAC: 5.3 (0.5–59) PIM: 3.5 (0.4–31) TCS: 4.9 (0.6–36)
Non-Hodgkin lymphoma	Untreated dermatitis: reference group TAC: 1.4 (0.5–4.0) PIM: 1.6 (0.8–3.5) TCS: 1.1 (0.5–2.1)
Selected non-T-cell lymphomas in a broad population ¹⁷ (duration of TCI use not evaluable)	
Hodgkin lymphoma	No TCS or TCI: reference group Duration of TCS use: < 30 days: 1.2 (0.9–1.8) 1–6 months: 1.9 (1.4–2.7) 6 months–1 year: 1.9 (0.8–4.5) 1–2 years: 2.2 (0.9–5.4) > 2 years: 9.6 (1.7–56)
B-cell non-Hodgkin lymphoma	No TCS or TCI: reference group Duration of TCS use: < 30 days: 1.2 (0.8–1.7) 1–6 months: 1.6 (1.1–2.3) 6 months–1 year: 1.9 (1.0–3.8) 1–2 years: 1.2 (0.4–3.7) > 2 years: 0
B-cell lymphoma in patients with atopic dermatitis or eczema ¹⁸ (TAC: 2.4 years follow-up; PIM: 1.9 years follow-up)	No TCI: reference group TAC: 1.1 (0.6–2.1) PIM: 1.6 (1.0–2.6)
All lymphoma	
All lymphoma in claims-based AD ²³ (TCI exposure duration not reported)	No TCI or TCS: reference group PIM: 0.8 (0.4–1.6) PIM + TCS: 1.1 (0.4–2.6) TAC: 0.8 (1.4–1.7) TAC + TCS: 0.9 (0.4–2.2) TCS high potency: 1.2 (0.8–1.8) TCS low potency: 1.1 (0.7–1.6) TAC ≤ 60 g: reference group TAC 61–90 g: 0.0 – TAC > 90 g: 0.2 (0.0–2.3) PIM ≤ 60 g: 0.7 (0.2–2.1) PIM 61–100 g: 0.2 (0.0–2.1) PIM > 100 g: 1.4 (0.3–6.4) TCS < 1 year: reference group TCS 1–2 years: 0.9 (0.6–1.5) TCS > 2 years: 0.7 (0.4–1.3) PIM < 1 year: 0.7 (0.3–1.6) PIM 1–2 years: 2.2 (0.9–5.8) PIM > 2 years: 1.7 (0.5–5.9) TAC: not reported by duration of use Untreated dermatitis: reference group TAC: 2.0 (0.9–4.5) PIM: 1.8 (0.9–3.5)
Lymphoma in broad population ¹⁶ (TAC: < 2 years use for 67% of exposed controls; PIM: < 2 years use for 71% of exposed controls)	

CI, confidence interval; AD, atopic dermatitis; TAC, tacrolimus; PIM, pimecrolimus.

as eczema in electronic codes, the impact of such reverse causation was addressed by the researchers who excluded people with malignancies in the first 6 months of follow-up.

All lymphomas

Atopic dermatitis

Fourteen studies reported results for all lymphoma or non-Hodgkin lymphomas grouped together. Because the validity of AD classification may vary by the method with which AD is ascertained,¹³ we include in Table 2 a description of AD ascertainment and whether AD or eczema status was medically confirmed or patient-reported. Across the six studies that ascertained AD or eczema with some level of medical input,^{17,20,22,23,25,26} the relative risk estimates for AD or eczema and lymphoma were all near 2. Three studies^{17,23,34} indicate that referral to a dermatologist, frequent health care for AD or hospitalization for AD are associated with 2.4-fold or greater risk of lymphoma.

If the association of AD and lymphoma stemmed from early treatment of lymphoma cutaneous symptoms as eczema, incidence of lymphoma immediately following the diagnosis of AD should be higher. Studies that excluded the first 6 months of follow-up should show lower RRs than those that did not exclude this early period. Unfortunately, none of the available studies provided data to assess directly the risk of lymphoma as a function of follow-up time from index AD diagnosis.

To assess the effect of symptomatic treatment of undiagnosed CTCL on the observed relative risk for lymphoma associated with AD, we conducted a bias analysis. We used the incidence of T-cell lymphomas,³⁵ cutaneous lymphomas³⁶ and lymphomas from population-based data in the U.S.A., and data on population prevalence of a claim for AD diagnosis from Arellano *et al.*²³ Figure 1 shows the observed relative risks for AD and lymphoma if the true relative risk is 1.0 and over a range of values for the proportion of CTCL that is undiagnosed and receives symptomatic treatment. The figure

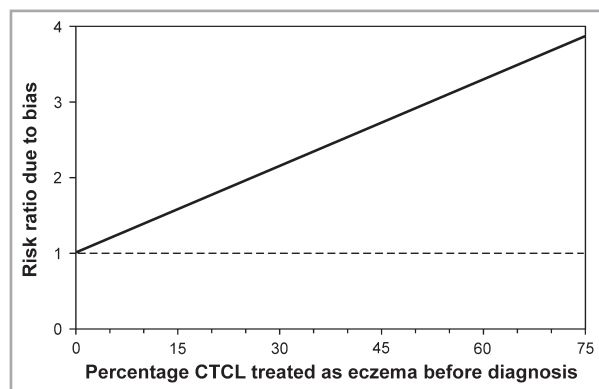


Fig 1. Risk ratio for lymphoma associated with atopic dermatitis as a function of percentage of cutaneous T-cell lymphoma (CTCL) with early symptoms treated as eczema when the true relative risk is 1.0.

shows that this symptomatic treatment could lead to substantial overestimation of the relative risk for lymphoma and AD (example calculations are shown in Table S2; see Supporting Information).

Use of topical calcineurin inhibitors

Arellano *et al.*²³ reported ORs for lymphoma and TCI use < 1.0 , and Schneeweiss *et al.*¹⁶ reported RRs > 1.0 (Table 3). Both studies had wide CIs. No conclusion about TCI use and risk of all lymphoma could be drawn.

Nonmelanoma skin cancer

Atopic dermatitis

Four studies^{22,34,37,38} evaluated the association between AD and nonmelanoma skin cancer (NMSC) (Table S3; see Supporting Information). Two studies conducted in dermatology outpatient clinics at a single institution reported an OR for AD based on diagnostic criteria and NMSC of 0.8 (95% CI 0.6–1.0)³⁴ and 0.4 (95% CI 0.3–0.5).³⁷ One of these studies³⁴ selected NMSC cases and controls from the clinical records; controls had diagnoses of warts, seborrhoeic keratosis, acne rosacea and dermatophyte infection. Because controls are likely to have been at the clinic and received longer dermatological treatments for various conditions than cases entering the system when their skin cancer was diagnosed, this study may underestimate the relative risk for NMSC and AD. The other study³⁷ selected controls from a cohort with dermatitis and is less susceptible to this bias.

Two cohort studies^{22,38} reported increased incidence of NMSC among patients hospitalized with a discharge code for AD. However, cohorts of patients treated by a dermatologist and hospitalized for AD may receive greater cutaneous surveillance associated with regular care for AD. The RRs reported from these studies may also be confounded by cutaneous surveillance associated with prior treatments such as tars or light therapy or by severity of AD.

Use of topical calcineurin inhibitors

One case-control study reported a negative association (OR 0.5; 95% CI 0.4–0.7) between NMSC and use of TCIs.³⁷ The results are consistent with the hypothesis that TCI use is negatively associated with NMSC, as are data from animal models.^{39–41} These results, however, are also consistent with selective prescribing of TCIs to patients least likely to develop skin cancer. Participation among controls was 62% and among cases, 70%, so selection bias cannot be precluded. The authors conducted several analyses to evaluate the magnitude of residual bias. They found that an uncontrolled confounder would have to be eight times more prevalent in controls than cases and associated with 10-fold increased risk to generate this level of negative association if the true relative risk for TCI use and NMSC were 2.0.

Melanoma

Two studies found no evidence that melanoma occurrence was associated with a primary inpatient diagnosis of AD (RR 0.6; 95% CI 0.3–1.2)²² or with use of tacrolimus (RR 0.3; 95% CI 0.1–0.8) or pimecrolimus (RR 0.7; 95% CI, 0.4–1.3).¹⁸

Discussion

Understanding the relation between AD, treatment of AD with TCIs, and risk of specific cancers poses significant scientific challenges. Randomized studies would need many arms, be extremely large and of long duration, and are subject to substantial loss to follow-up. Alternatively, pharmacoepidemiological studies are more feasible but pose their own challenges. Teasing apart possible causal roles of AD and TCIs in lymphoma and skin cancer exemplifies the classic pharmacoepidemiological problem of confounding by indication, where the disease being treated may increase the risk of the outcome under study. If the treatment is used largely for that one indication, it may be nearly impossible to disentangle the effects of treatment from those of the disease. If, as in this case, a variety of cancers constitutes the possible outcomes, the task may be even more challenging.

In trying to distinguish between effects of AD and effects of TCIs on the cancers mentioned, we searched for studies that addressed at least one specific aspect and looked for hypothesized relations that would separate potentially causal from noncausal relations. Given the combinations of exposure (TCIs and AD that meets diagnostic criteria, having administrative diagnostic codes for AD, or self-reported eczema) and outcome (five categories of cancers) to be addressed, the literature was bound to have gaps. Nevertheless, our review allows some limited statements about AD, TCIs and specific cancers, and helps to highlight the gaps that remain.

We found that relative risk of all lymphoma associated with AD or eczema ranged from 0.7 to 1.8 when measured in a variety of study populations with AD or eczema, and from 2.0 to 3.7 when measured in individuals with indicators for severe AD (see Table 2). The greater association between lymphoma and severe AD is consistent with the hypothesis that risk of lymphoma may be associated with the disease process for AD or with its treatment or both.

The few patients exposed to TCIs and the comparatively short duration of TCI treatment, generally 2 years or less, precluded definitive evidence to document a causal role of TCI use, as a class or individually, in the development of specific lymphomas. The single study that showed a strong, although imprecise, association with TCIs and Hodgkin lymphoma also demonstrated a similarly strong association of TCS and Hodgkin lymphoma. The strong association between duration of TCS use and non-Hodgkin lymphoma is also consistent with the hypothesis that nonspecific cutaneous symptoms of lymphoma may also be treated with eczema treatments. Furthermore, the low systemic exposure to

TCIs^{42,43} makes it less plausible that TCI use causes nonskin cancer. The short follow-up in the few cohort studies did not permit the evaluation of an effect on cancer risk after a long induction time.

CTCL may be treated topically as a dermatitis for 6 months to 10 years or longer^{44,45} before diagnosis, and symptomatic treatment of undiagnosed CTCLs could result in an increased association of AD or eczema care and lymphoma with increased duration of follow-up. There are no data to support or refute this hypothesis. However, in one study, charts for four of 16 TCI-exposed CTCL cases contained mentions of suspected CTCL at the time of TCI initiation.¹⁸ In the insurance claims setting, the lack of an appropriate insurance code for ruling out CTCL may result in using a dermatitis code. Our simple model assuming treatment of early symptoms of some undiagnosed CTCLs showed high apparent relative risks for AD or eczema measures and CTCL. Because probability of early treatment as AD or eczema will vary by type of lymphoma, grouping of lymphomas may introduce bias.

Errors from patient self-report of eczema, although theoretically a concern, have only a small effect on relative risks between AD or eczema and cancers. Errors in measuring TCI use based on pharmacy claims or electronic medical records contribute to underestimation of effects. Such errors could be mitigated by focusing on prescription refills. All identified studies included predominantly patients with short-term and low exposure to TCIs (in one study, 83% used ≤ 2 tubes³⁷ and in another the median duration of use was < 1 year¹⁶). Consequently, little can be inferred about the effect of longer TCI use.

We found no evidence that melanoma or NMSC is associated with TCI use. Nevertheless, surveillance bias in cohort studies and referral bias in some case-control studies pose additional challenges in interpreting the existing literature on skin cancers.

What are the implications of these results for current clinical practice? Physicians need to weigh risks against benefits. For AD, physicians find themselves attempting to balance the therapeutic benefit against the hypothetical increased risk of malignancy. This judgment, difficult even if risks and benefits are precisely measured, is much more difficult when the increased risks for malignancy are uncertain and could possibly be zero. It seems reasonable to say that the hypothesis that pimecrolimus and tacrolimus cause malignancy, which was based on preclinical animal models and spontaneous case reports, has not been supported by the epidemiological studies to date, which were conducted in a variety of patient populations. Thus, current data, although meagre, are reassuring with respect to cancer risk associated with these medications as they are used in clinical practice.

Unfortunately, the existing data are inadequate to settle the question. Better studies would require larger numbers of patients and longer exposure to TCIs. Such data are not available for any of the existing therapies for AD or eczema, some of which (TCS) have been in use for over 50 years. Unless

and until these studies are forthcoming, physicians will have to continue to weigh reliable treatment benefits against potential long-term risks.

What's already known about this topic?

- Atopic dermatitis may be associated with lymphoma and skin malignancies stemming from the disease itself or from several of its treatments, which can be mutagenic or immunosuppressive.
- Some animal models and case reports have prompted the hypothesis that topical calcineurin inhibitors (TCIs) may increase the risk of skin cancer and lymphoma.

What does this study add?

- The hypothesis that TCIs cause malignancy is not well supported by the few existing epidemiological studies, but the total number of exposed patients in these studies is too small to exclude the possibility that there is a moderately increased risk associated with TCIs. There are few recorded cases of any specific malignancy among dermatological patients exposed to TCIs, and therefore the associations between TCIs and specific malignancies are all imprecisely measured.
- Among patients hospitalized for atopic dermatitis, the plausible level of diagnostic bias that stems from routine dermatological surveillance could account for an increase in diagnosis of nonmelanoma skin cancer.

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Supporting Information

Additional Supporting Information may be found in the online version of the article:

Data S1. Search terms used in literature search.

Table S1. Hypotheses regarding factors that could impact the observed association between atopic dermatitis (AD) or topical calcineurin inhibitors (TCIs) and lymphomas or skin cancers.

Table S2. Example derivation of risk ratio for lymphoma associated with atopic dermatitis when cutaneous T-cell lymphoma is initially unrecognized and treated as atopic dermatitis/eczema.

Table S3. Studies that evaluated atopic dermatitis or topical calcineurin inhibitor use as a risk factor for skin cancers in dermatology populations.

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