Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: A systematic review and meta-analysis

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Background: There is controversy regarding a potential increased risk of lymphoma in patients with atopic dermatitis (AD).

Objective: To assess the risk of lymphoma and the role of topical treatments in patients with AD.

Methods: A systematic literature search and a separate meta-analysis were performed on case control and cohort studies.

Results: Of the 3979 articles retrieved, 24 references met the inclusion criteria. In cohort studies, the risk of lymphoma was slightly increased, with a relative risk (RR) of 1.43 (95% confidence interval [CI], 1.12-1.81). In case control studies, no significant increased risk of lymphoma was found, with an odds ratio (OR) of 1.18 (95% CI, 0.94-1.47). Severity of AD was a significant risk factor. Highly potent topical steroids were associated with an increased risk of lymphoma. For topical calcineurin inhibitors (TCIs), a significant association between tacrolimus and mostly skin lymphoma was found in 1 study.

Limitations: Confusion between severe AD and cutaneous T-cell lymphoma may account for part of the increased risk of lymphoma in patients with AD.

Conclusion: This systematic literature review shows a slightly increased risk of lymphoma in patients with AD. Severity of AD appears to be a significant risk factor. The role of topical steroids and TCIs is unlikely to be significant. (J Am Acad Dermatol 2015;72:992-1002.)

Key words: atopic dermatitis; lymphoma; neoplasm; pimecrolimus; systematic review; tacrolimus; topical corticosteroids.

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects approximately 15% of children in Western countries[1] and 2% to 3% of adults.[2] The risk of lymphoma in patients with AD is debated. Isolated cases of lymphoma in adult patients with AD have been reported in the literature.[3,4]

There are multiple confounding factors that make the interpretation of an increased risk of lymphoma

Abbreviations used:

AD:	atopic dermatitis
CI:	confidence interval
CTCL:	cutaneous T-cell lymphoma
OR:	odds ratio
RR:	relative risk
SIR:	standardized incidence ratio
TCI:	topical calcineurin inhibitor
TCS:	topical corticosteroid

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in patients with AD difficult. Topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs) have been associated with potential systemic effects and reduced immunosurveillance.[5]

The primary objective of this systematic review was to evaluate if patients with AD have a higher background risk of lymphoma than the general population. The secondary objective was to evaluate if treatment with TCSs or TCIs may influence the risk of lymphoma in patients with AD.

CAPSULE SUMMARY

- There is controversy about the risk of lymphoma in patients with atopic dermatitis.
- There is a small increased risk of lymphoma in patients with atopic dermatitis.
- Highly potent steroids but not topical calcineurin inhibitors are associated with lymphoma risk.
- Classification bias between severe atopic dermatitis and cutaneous T-cell lymphoma is an issue.
- Cutaneous T-cell lymphoma should be ruled out in patients with adult onset severe atopic dermatitis. Patients should be reassured about the safety of topical calcineurin inhibitors with regard to lymphoma risk.

METHODS

Systematic literature search

We performed a systematic review of original studies investigating the risk of lymphoma in patients with AD published between 1980 and February 28, 2014. The Cochrane, PubMed, and Scopus databases were systematically searched. The literature search used the following combination of Medical Subject Headings (MeSH): "atopic dermatitis AND lymphoma." A second combination was systematically searched in the same databases: "atopic dermatitis AND neoplasm." A third combination was systematically searched in the same databases in November 2014: "eczema AND lymphoma" and "eczema AND neoplasm." We limited the literature search to articles on human subjects that were written in English, French or German.

To evaluate the reporting quality of publications, we used the Newcastle–Ottawa scale[6] and the Reporting of Observational Studies in Epidemiology criteria.[7]

Reference lists from selected articles were systematically reviewed for additional studies not retrieved by the database search. When data from articles were missing to calculate odds ratios (ORs) and relative risk (RR), we contacted the corresponding author of the paper to obtain the original data.

Data extraction and analysis

We extracted the following data: type of database, year of publication, author, study design, number of patients with AD, number and origin of controls, follow-up period, type of lymphoma (ie, skin/nonskin, Hodgkin/non-Hodgkin), and AD severity. Exposure to TCSs and TCIs were recorded when available.

The systematic electronic searches and data extraction were independently performed by 2 reviewers (L.L. and C.P.). All disagreements on which studies to select were reviewed by the 2 reviewers to reach final agreement.

In each selected study, the effect size criteria and its confidence interval (CI) were searched. When available, the number of events was used to calculate effect size estimators. Several estimators were identified: OR for case control studies or cross-sectional studies and RR for cohort studies. Meta-analyses were performed only on homogeneous studies according to their estimators to minimize the heterogeneity.

To compute data issued from the selected studies, we used the generic inverse variance approach. Estimates and their standard errors were entered directly as natural logarithms (ie, as a log odds ratio and the standard error of the log odds ratio). The software undertook fixed-effect meta-analyses and random effects (Der Simonian and Laird) meta-analyses, along with assessment of heterogeneity. Risk estimator and 95% CI were shown on forest plots. Statistical heterogeneity of studies considered was assessed on the basis of the Q test (χ^2), using a significance level of .05. The I^2 statistic was presented with high values, indicating high heterogeneity.[8] The nature of the statistical model selected (fixed or random effect) was presented on the top of each forest plot, based on the result of Cochrane Q test, with the label "fixed" or "random." Publication bias was assessed using the Egger test.

All computations were performed using the Revman software package developed by the Nordic Cochrane centre (v 5.1; The Nordic Cochrane Centre, Copenhagen, Denmark). $P < .05$ was considered statistically significant.

RESULTS

From an initial selection of 2046 references, 2019 articles were excluded after reading the title or