

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 <http://dx.doi.org/10.1016/j.jaad.2015.02.1116>.)

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 countries¹ 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.

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 scale⁶ 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

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.

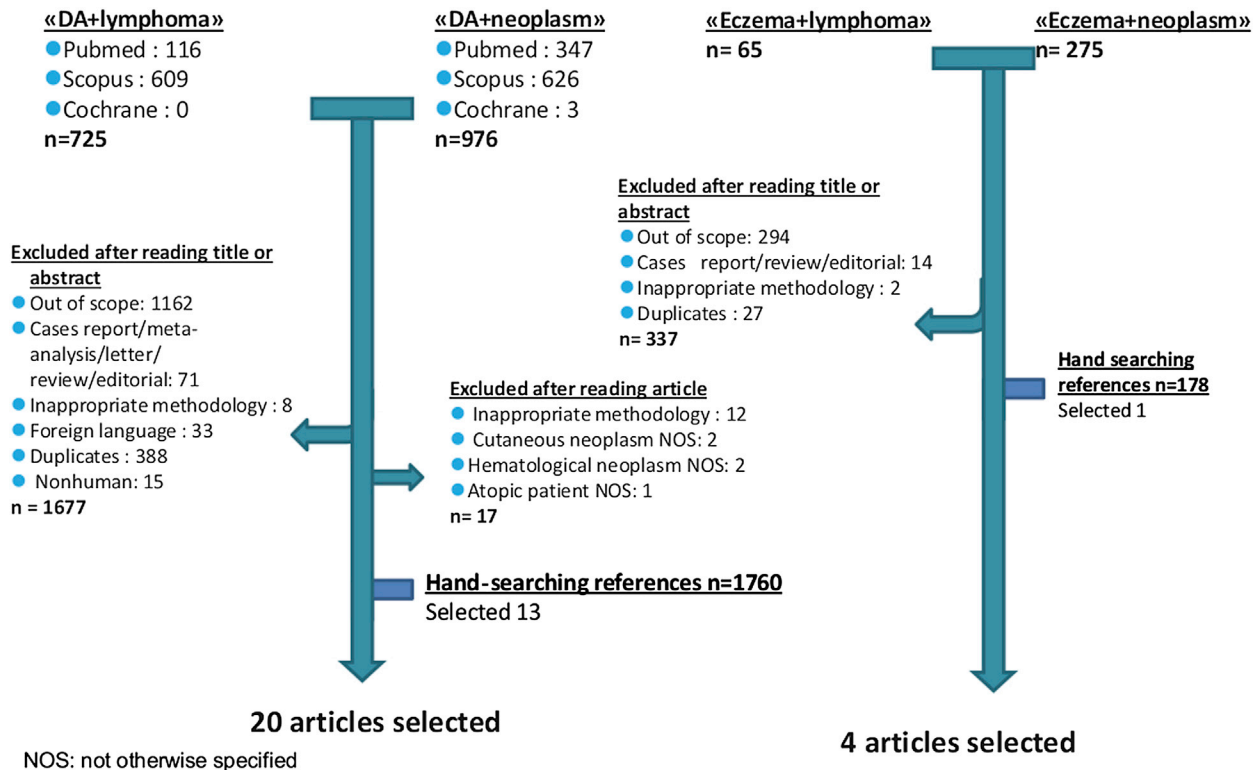


Fig 1. Flow chart of study selection process.

abstract and 17 were excluded after reading the article. Fourteen articles were added by searching references lists from selected articles. In total, 24 references were retained. The study selection process is summarized in Fig 1. A systematic quantitative evaluation of the Newcastle–Ottawa scale was performed. According to this scale, the maximum number of quality stars a study publication can obtain is 9. The average number of stars recorded for cohort studies was 6.5 (range, 5–8). The average number of stars recorded for case control studies was 6.3 (range, 4–8). The Egger test did not indicate significant publication bias either for cohort ($P = .280$) or case control studies ($P = .697$).

AD and the risk of lymphoma

Twenty-three studies were selected^{9–30} (Table I): 5 cohort studies and 18 case control studies. Four cohort studies computed relative risk of lymphoma. One cohort study in patients hospitalized for AD in Sweden¹⁷ computed standardized incidence ratio (SIR) and found an increased risk of lymphoma associated with AD with a SIR of 2.0 (95% CI, 1.4–2.9). A total of 29 AD patients out of 1566 experienced a lymphoma in the registry. Lymphoma cases were identified by the National Swedish Cancer Register and coded as lymphoma according to the *International Classification of Diseases, 7th edition*

classification (codes 200–202) during the entire period of the study. Two additional cohort studies^{19,23} reported an increased RR of lymphoma in patients with AD. Among the case control studies (Table I), 5 showed a higher risk of lymphoma associated with AD.^{10,11,13,20} Two case control studies^{12,15} found a significant reduction in the risk of lymphoma associated with AD. Eleven studies showed no increased risk of lymphoma in patients with AD.^{14,16,18,21,24–30}

A meta-analysis was conducted including the 4 cohort studies estimating RR^{9,19,22,23} (Fig 2). Three of 4 studies were performed in automated databases: 2 from the United States (Medicaid¹⁹ and Ingenix Research Data Mart²²) and 1 from the United Kingdom (The Health Improvement Network database [THIN]⁹). The diagnosis of AD or dermatitis was confirmed by using various combinations of ICD codes with little consistency between studies.^{9,19,22} In 1 population-based cohort study from the Swedish twins registry, the diagnosis of AD was made retrospectively by evaluating responses to a standardized questionnaire.²³ In 4 studies, the diagnosis of lymphoma was confirmed using relevant ICD codes in the databases^{9,19,22} and in the Swedish cancer registry.²³ In database studies, the follow-up of patients was relatively short, varying from 1.3 to 6.8 years for 3 studies.^{9,19,22} The duration of follow-

Table I. Studies selected estimating the risk of lymphoma in patients with atopic dermatitis

Author, year, study design	No. of patients	No. of controls	Date of inclusion or mean follow-up	Main results (95% CI)
Arana et al, ⁹ 2010, cohort	66,258 patients with AD	4,389,750 subjects without AD	January 1, 1992 to March 23, 2006; follow-up 6.78 years	RR = 1.21 (0.90-1.63)
Arellano et al, ¹⁰ 2007, case control	294 cases of lymphoma	1176	July 1995 to January 2005	OR = 2.41 (1.86-3.12)
Arellano et al, ¹¹ 2009, case control	2738 cases of lymphoma	10,949	January 1, 1992 to March 23, 2006	OR = 1.84 (1.44-2.35)
Bernstein et al, ¹² 1992, case control	619 NHL	282 male matched pairs and 337 female matched pairs	January 1, 1979 to June 30, 1982	OR = 0.60 (0.38-0.95)
Cartwright et al, ¹³ 1988, case control	437 cases NHL	724	October 1979 to December 1984	OR = 1.98 (1.33-2.95)
Cerhan et al, as reported by Vajdic et al, ³¹ case control	440 cases of NHL	453	2002 to 2005	OR = 1.69 (1.03-2.76)
Cozen et al, ¹⁴ 2007, case control	604 cases of NHL	464	July 1, 1998 to June 30, 2000	OR = 1.15 (0.74-1.79)
Doody et al, ²⁷ 1992, case control	100 cases of NHL	191	1959 to 1979	OR = 1.98 (0.67-5.81)
El-Zein et al, ³⁰ 2010, case control	197 cases of NHL	512	August 1979 to March 1986	OR = 1.70 (0.61-4.78)
Fabbro-Peray et al, ¹⁵ 2000, case control	517 cases of lymphoma	1025	January 1, 1992 to December 31, 1995	OR = 0.45 (0.31-0.65)
Grulich et al, ¹⁶ 2005, case control	704 cases of NHL	694	January 2000 to August 2001	OR = 0.78 (0.56-1.09)
Hagströmer et al, ¹⁷ 2005, cohort	15,666 cases of AD		January 1, 1965 to December 31, 1999; follow-up of 15.4 years	SIR = 2.0 (1.4-2.9)
Holly et al, ¹⁸ 2003, case control	1304 cases of NHL	2402	1988 to 1995	OR = 1.34 (0.93-1.93)
Margolis et al, ¹⁹ 2001, cohort	3869 cases of severe eczema		1992 to March 1996; mean follow-up for severe eczema 2.27 years	RR = 1.95 (1.15-3.31)
Melbye et al, ²⁰ 2007, case control	3055 cases of NHL	3187	October 1, 1999 to August 30, 2002	OR = 1.30 (1.05-1.61)
Morales et al, ²¹ 2003, case control	76 cases of mycosis fungoides	2904	1995 to 1998	OR = 1.34 (0.72-2.49)
Rudant et al, ²⁹ 2011, case control	128 cases of HL, 164 cases of NHL	1312	2003 to 2004	OR = 0.96 (0.65-1.43)
Schneeweiss et al, ²² 2009, cohort	1,200,645 patients treated with TCI or corticosteroids	118,825 patients with untreated dermatitis and 118,863 people from the general population	January 1, 2002 to June 30, 2006; follow-up of 1.3 years	RR = 1.40 (0.53-3.70)
Söderberg et al, ²³ 2004, cohort	400 cases with eczema during childhood		January 1, 1969 to December 31, 1999; follow-up of 23 years for men and 27 years for women	OR = 2.43 (1.07-5.52)
Tuyp et al, ²⁴ 1987, case control	53 cases of mycosis fungoides	53	Unknown	OR = 2.04 (0.18-23.12)
Vadjic et al, ²⁸ 2007, case control	694 NHL	694	2000 to 2001	OR = 0.71 (0.49-1.04)
Vineis et al, ²⁵ 2000, case control	2669 cases of lymphoma	1718	1990 to 1993	OR = 1.00 (0.80-1.25)
Zhang et al, ²⁶ 2004, case control	601 NHL	717	January 1996 to June 2000	OR = 1.17 (0.81-1.69)

OR, Odds ratio; RR, relative risk; SIR, standardized incidence ratio.

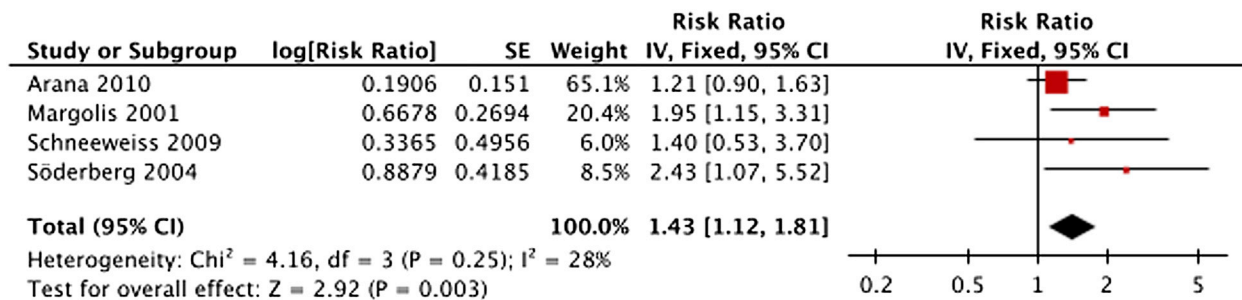


Fig 2. Overall risk ratio of lymphoma: meta-analysis of cohort studies.

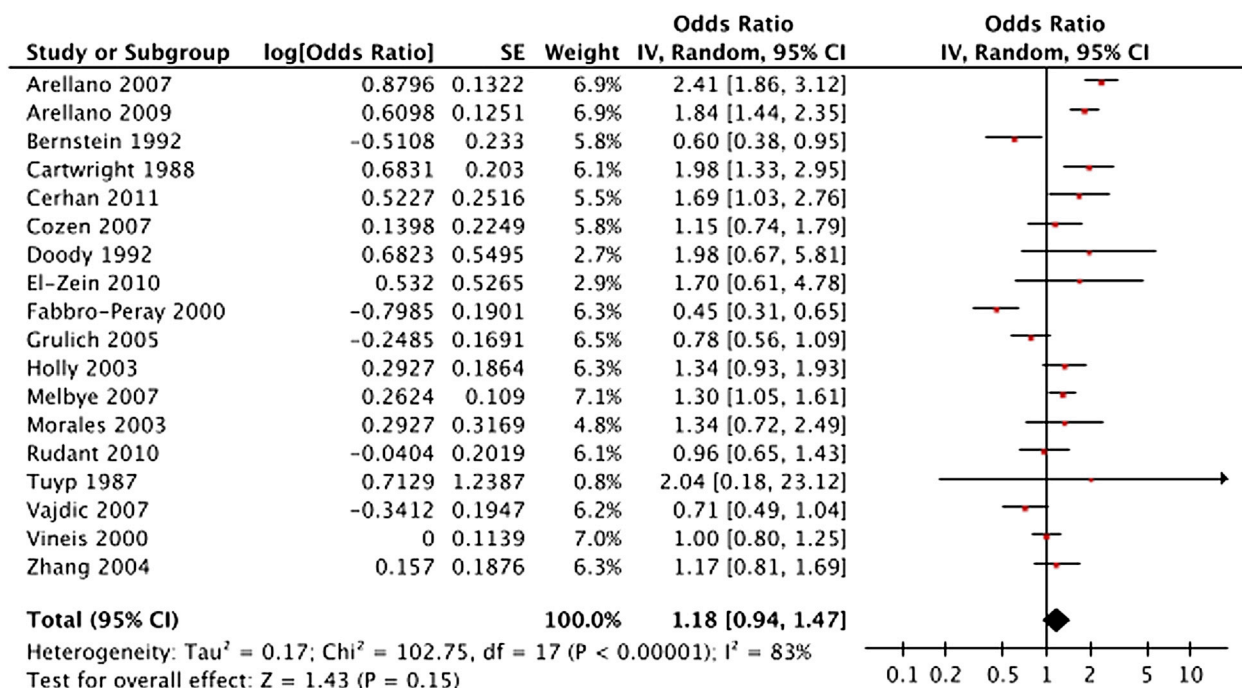


Fig 3. Overall odds ratio of lymphoma: meta-analysis of case control studies.

up in the study by Söderberg et al²³ was 23 years for men and 27 years for women. The number of AD/eczema patients evaluated in cohort studies varied between 1033 and 4,518,131. The meta-analysis found an overall RR of 1.43 (95% CI, 1.12-1.81), indicating a significant increased risk of lymphoma associated with AD/eczema. The heterogeneity was not significant ($I^2 = 28\%$; $P = .25$).

All 18 case control studies were included in a meta-analysis^{10-16,18,20,21,24-31} (Fig 3). Two of them had chosen a combination of codes for the diagnosis of AD: by the presence of codes 691 and 692 in ICD in the PharMetrics database in 1 study¹⁰ and in the THIN study by the presence of READ codes M11.00, M11.z, and M111-117.¹¹ One study chose medical record summaries.²⁷ Fifteen studies used interview or questionnaires to establish the diagnosis of AD: 2 studies chose phone interviews,^{20,29} 2 studies used

face to face interviews,^{18,25} 2 studies used questionnaires completed by patients,^{28,31} 3 studies interviews with the help of a standardized questionnaire,^{12,21,26} 1 study interview by 1 dermatologist,²⁴ 3 studies an interview without more information,^{13,14,30} 1 study face to face interview and/or phone interview,¹⁵ and 1 study combination of a questionnaire and a phone interview.¹⁶

Identification of lymphoma cases was validated through individual medical records and pathology review in 15 studies. In 1 study,¹² the diagnosis of lymphoma was supported by data from the Cancer Surveillance Program, the population-based cancer registry of Los Angeles County (CA) and in 1 study by data from the Kaiser Permanente Medical Care Programme (US).²⁷ In 1 study, histologic subtypes of Hodgkin and non-Hodgkin lymphoma were obtained from investigators.²⁹

Table II. Studies selected showing association between severity of atopic dermatitis and risk of lymphoma

Author, years	Study design	Risk	95% CI	Percent of cutaneous lymphoma
Arellano et al, ¹⁰ 2007	Case control	OR adjusted = 2.4	1.5-3.8	18.4
Arellano et al, ¹¹ 2009	Case control	OR adjusted = 3.72	1.40-9.87	6.87
Margolis et al, ¹⁹ 2001	Cohort	RR = 1.95	1.15-3.31	Unknown

CI, Confidence interval; OR, odds ratio; RR, relative risk.

Table III. Studies selected estimating the risk of lymphoma with pimecrolimus treatment

Author, year	Study design	No. of subjects	Duration of exposure	Main results
Arellano et al, ¹¹ 2009	Case control	2738 cases of lymphoma (5%) occurred in 3,500,194 individuals; 113 initiators of pimecrolimus	Unknown	0 cases of lymphoma
Arellano et al, ¹⁰ 2007	Case control	294 cases of lymphoma occurred in 293,253 patients; 14 initiators of pimecrolimus	Unknown	OR = 0.85 (0.47-1.55)
Hui et al, ³² 2009	Cohort	22,716 with only topical pimecrolimus, 4068 with tacrolimus and pimecrolimus	1.7 y	RR = 1.47 (0.47-4.66)
Schneeweiss et al, ²² 2009	Cohort	118,863 initiators of pimecrolimus	1.5 y	RR = 1.63 (0.75-3.54)

OR, Odds ratio; RR, relative risk.

The origin of subjects varied: 5 studies were performed in the United States,^{10,12,14,18,27} 4 studies in the United Kingdom,^{11,13,26,31} 5 studies in Western Continental Europe,^{15,20,21,25,29} 2 studies in Australia,^{16,28} and 1 study in Canada.³⁰ In 1 case control study, the origin of subjects was not specified.³¹ The overall OR for lymphoma in patients with AD was 1.18 (95% CI, 0.94-1.47), showing no significant increased risk. The heterogeneity was high ($I^2 = 83\%$; $P < 10^{-4}$).

Influence of severity

Three studies evaluated the influence of AD severity on the risk of lymphoma^{10,11,19} (Table II). These were 2 case control studies and 1 cohort study. In all studies, medical care resource use was used as a surrogate marker of AD severity. In 1 study, a patient was classified as having severe eczema if he/she consulted a physician on at least 4 occasions in a 12-month period.¹⁹ In 1 UK study, severe AD was defined as attending at least 4 physician visits for AD per year in patients ≥ 3 years of age. For patients < 3 years of age, having attended at least 1 visit to a dermatologist in the follow-up period was the criterion used to define severe AD.¹⁰ In the third study, patients with a diagnosis of AD who were referred to a dermatologist were considered as having severe AD.¹¹

A significant association between lymphoma and severity of AD was found in all 3 studies. In the 2 case

control studies, the adjusted OR of lymphoma in patients with severe AD varied from 2.4 (95% CI, 1.5-3.8)¹⁰ to 3.72 (95% CI, 1.40-9.87).¹¹ In the cohort study, the RR was 1.95 (95% CI, 1.15-3.12).¹⁹

Influence of treatments: TCIs and TCSs

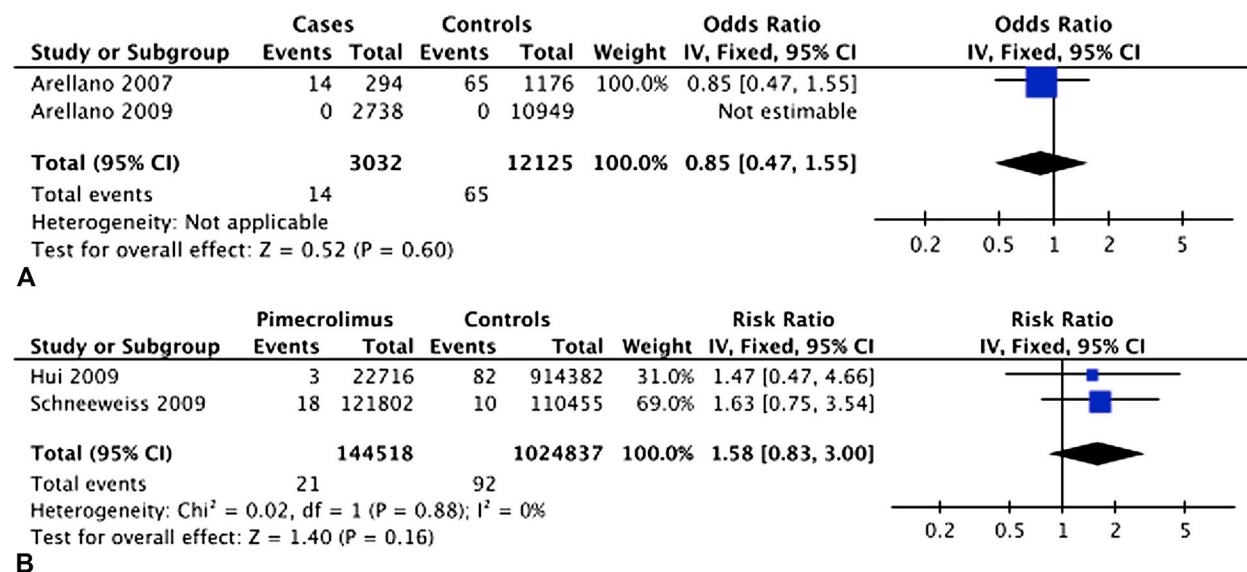
Four studies evaluated the role of TCIs in the development of lymphoma in patients with AD. These were 2 case control studies^{10,11} and 2 cohort studies^{22,32} (Table III). The main characteristics of these studies are summarized in Tables III and IV.

One study from the United States performed in the Kaiser Permanente database found an increased risk of lymphoma associated with the prescription of TCIs.³² In this study by Hui et al,³² the RR of lymphoma associated with tacrolimus was 6.56 (95% CI, 3.03-14.19). This association was entirely explained by an increased risk of T-cell lymphoma (TCL) in subjects exposed to tacrolimus, with a hazard ratio of 5.44 (95% CI, 2.51-11.79; $P < .001$). A proportion of 81% of TCL reported in TCI users were cutaneous TCL (CTCL). For pimecrolimus, the risk of TCL was not significantly increased, with a hazard ratio of 2.32 (95% CI, 0.89-6.07; $P = .086$). No data on TCS use was provided in the article. The results of Hui et al's study³² were based upon 12 cases of lymphoma out of 953,064 patients with AD. The median cumulative amount of tacrolimus 0.1% ointment exposure was 75 g in patients with TCL and 60 g in the group without TCL. Concerning

Table IV. Studies selected estimating the risk of lymphoma with tacrolimus treatment

Author, year	Study design	No. of subjects	Duration of exposure	Main results
Arellano et al, ¹¹ 2009	Case control	2738 cases of lymphoma (5%) occurred in 3,500,194 individuals; 133 initiators of tacrolimus	Unknown	OR = 0.57 (0.03-11.06)
Arellano et al, ¹⁰ 2007	Case control	294 cases of lymphoma occurred in 293,253 patients; 11 initiators of tacrolimus	Unknown	OR = 1.08 (0.55-2.12)
Hui et al, ³² 2009	Cohort	11,898 with only topical tacrolimus, 4068 with tacrolimus and pimecrolimus	1.4 y	RR = 6.56 (3.03-14.19)
Schneeweiss et al, ²² 2009	Cohort	38,757 initiators of tacrolimus	1.5 y	RR = 1.36 (0.47-3.98)

OR, Odds ratio; RR, relative risk.

**Fig 4.** **A**, Meta-analysis estimating the risk of lymphoma with pimecrolimus in case control studies. **B**, Meta-analysis estimating the risk of lymphoma with pimecrolimus in cohort studies.

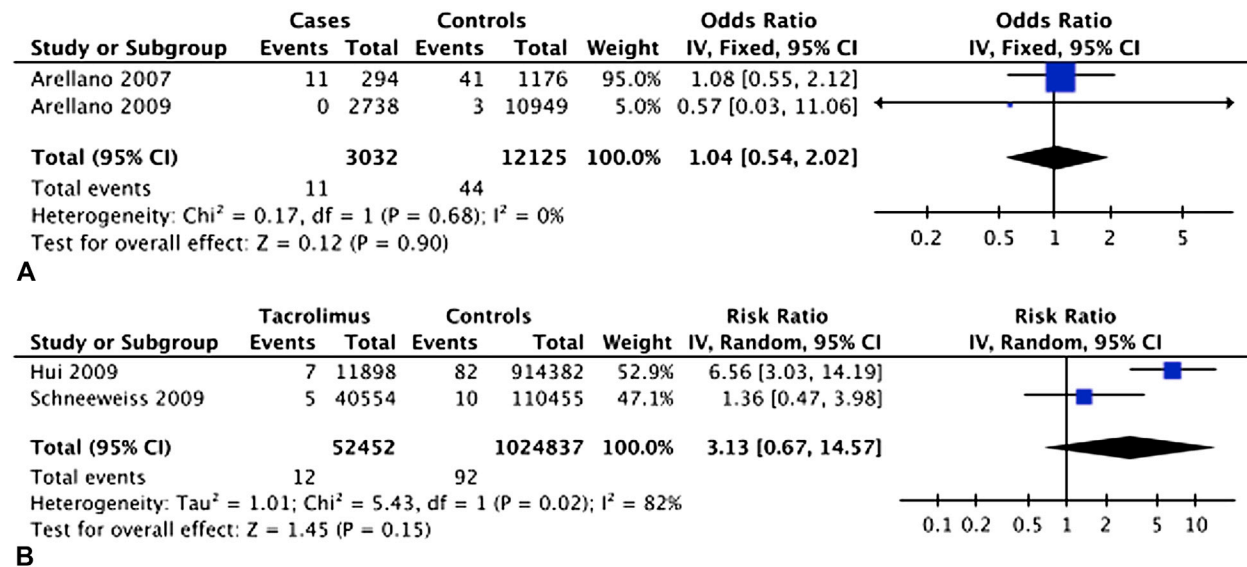
tacrolimus 0.03% ointment, this amount was 105 g in the group of patients with TCL and 60 g in the group of patients without TCL. For pimecrolimus, the median cumulative cream amount was 60 g.

In a study by Schneeweiss et al,²² the exposure to TCI was low in the majority of patients. Seven of 11 patients with lymphoma and 30 of 48 control patients had used <60 g of pimecrolimus cream. The same was true for tacrolimus ointment users: 12 of 13 patients with lymphoma and 36 of 49 controls had used <60 g of tacrolimus ointment.

A meta-analysis was conducted to determine the risk of lymphoma associated with pimecrolimus (Fig 4): the overall OR from case control studies was 0.85 (95% CI, 0.47-1.55), whereas the overall RR from cohort studies was 1.58 (95% CI, 0.83-3.00; $I^2 = 0\%$; $P = .88$). The same analysis was conducted with

tacrolimus (Fig 5): the overall OR from case control studies was 1.04 (95% CI, 0.54-2.02; $I^2 = 0\%$; $P = .68$), and the overall RR from cohort studies was 3.13 (95% CI, 0.67-14.57). Heterogeneity was high ($I^2 = 82\%$; $P = .02$). There was no significant increased risk of lymphoma associated with the use of TCIs.

Three studies evaluated the potential risk of lymphoma associated with TCSs: 2 case control and 1 cohort study.^{10,11,22} The primary characteristics of these studies are summarized in Table V. The 2 case control studies were included in a meta-analysis (Fig 6). There was a significantly increased risk of lymphoma associated with the use of high potency TCSs with an overall OR for lymphoma of 1.73 (95% CI, 1.52-1.97; $I^2 = 0\%$; $P = .68$). No increased risk was found with low potency TCSs, with an OR of 1.11 (95% CI, 0.80-1.54; $I^2 = 75\%$; $P = .04$).

**Fig 5. A**, Meta-analysis estimating the risk of lymphoma with tacrolimus in case control studies.**B**, Meta-analysis of cohort studies estimating the risk of lymphoma with tacrolimus treatment.**Table V.** Studies selected estimating the risk of lymphoma with topical corticosteroid treatment

Author, year	Study design	No. of subjects	Duration of exposure	Main results
Arellano et al, ¹¹ 2009	Case control	2738 cases of lymphoma (5%) occurred in 3,500,194 individuals (926 TCS: 238 high- and 641 low-potency)	Low potency: 580/641 used TCS <6 mo; high potency: 197/283 used TCS <6 months	Low-potency corticosteroids: OR = 1.28 (1.15-1.41); High-potency corticosteroids: OR = 1.75 (1.52-2.03)
Arellano et al, ¹⁰ 2007	Case control	294 cases of lymphoma occurred in 293,253 patients (133 with TCS: 72 high- and 61 low-potency)	Unknown	Low-potency corticosteroids: OR = 0.91 (0.66-1.24); High-potency corticosteroids: OR = 1.63 (1.20-2.22)
Schneeweiss et al, ²² 2009	Cohort	309,607 with medium or high-potency TCS initiators	1.4 y	RR = 1.16 (0.74-1.82)

OR, Odds ratio; RR, relative risk; TCS, topical corticosteroids.

DISCUSSION

This systematic review indicates a modest increase in the risk of lymphoma in patients with AD compared to the general population, although the heterogeneity in case control studies prevents us from drawing a definite conclusion. This increased risk appears to be statistically significant in the meta-analysis of cohort studies,^{9,19,22,23} with an overall RR of 1.43 (95% CI, 1.12-1.81). The use of highly potent TCSs was associated with a small increase in lymphoma risk, statistically significant in the meta-analysis of case control studies. There was no increased risk of lymphoma with TCIs.

AD severity appears to be a significant risk factor for lymphoma in patients with AD.^{10,11,19}

It should be taken into account that the high heterogeneity in study designs, populations, and analysis—particularly in case control studies—prevents a robust estimation of the risk of lymphoma in patients with AD. There was a high level of heterogeneity between studies regarding the definition of AD, lymphoma diagnostic validation, type of reference population, and follow-up. The use of administrative claim databases and/or diagnostic codes (as the *International Classification of Diseases for Oncology*) in many studies could be a source of coding errors and diagnosis misclassification, leading to potential bias.

It should be noted that the meta-analysis of case control studies showed high heterogeneity, with an I^2 statistic of 0.86 (Fig 3). This high heterogeneity

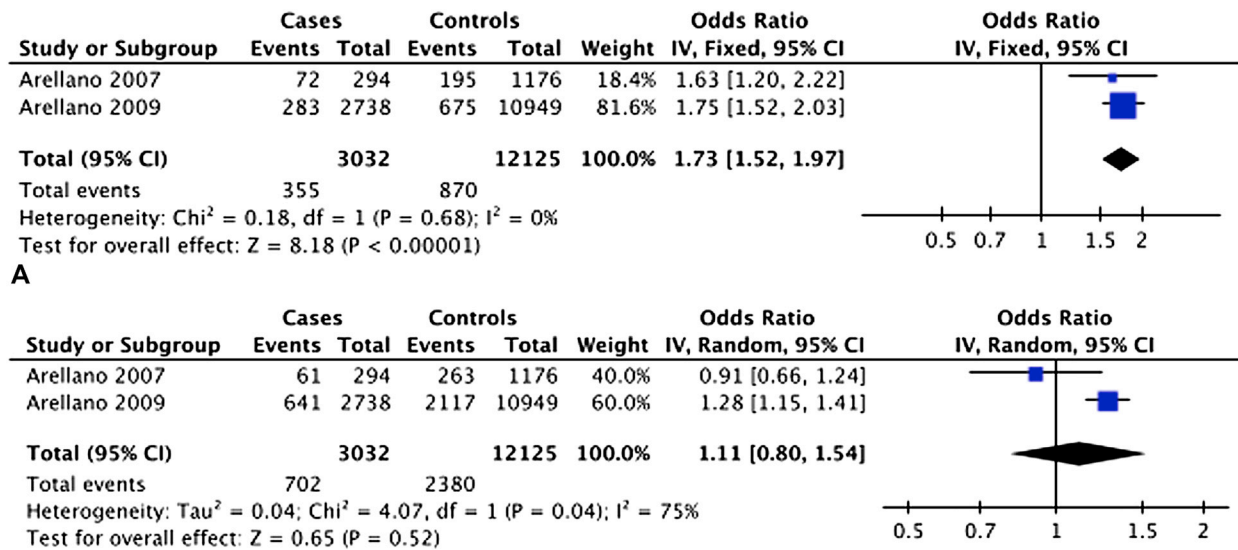


Fig 6. **A**, Meta-analysis estimating the risk of lymphoma with high potency topical corticosteroid treatment. **B**, Meta-analysis estimating the risk of lymphoma with low potency topical corticosteroid treatment.

suggests that the absence of association between AD and lymphoma found in case control studies is not a robust finding.

One important issue to be discussed is the association between CTCL and AD. The differential diagnosis between CTCL and AD is not always easy, and patients with CTCL can be diagnosed with AD and treated as such before the correct diagnosis is made.³³⁻³⁵ CTCLs represent <20% of the cases of extranodal lymphoma and about 29% of TCL cases in the general population based on Surveillance, Epidemiology, and End Results data.³⁶ Misclassification probably occurred in the study reported by Hui et al.³² There was an overrepresentation of patients with CTCL (81% of TCLs in the cohort of TCI users in their study). In the study by Schneeweiss et al,²² the proportion of cutaneous lymphoma varied between 19% and 30% in TCI users.

There is a high level of controversy regarding the potential contributing role of AD treatment on lymphoma risk. The statistical association between highly potent TCSs and the risk of lymphoma reported in 2 studies may have been confounded by AD severity.^{10,11} Highly potent TCSs are mostly used for the treatment of severe AD. In the case control study by Arellano et al,¹⁰ the increased risk of lymphoma observed with highly potent TCSs disappeared after adjusting for AD severity. The exposure to TCSs in the studies was low (<6 months-12 months), indicating that the causal relationship between high-potency steroid use and lymphoma is questionable (Table V).

TCIs were approved for short-term or chronic intermittent treatment of AD in patients >2 years of age and in whom other treatments were ineffective or contraindicated.³⁷ In 2006, the US Food and Drug Administration issued a black box warning regarding a potential increased risk of lymphoma associated with TCIs.³⁸

Human pharmacokinetic studies have concluded that the systemic absorption of TCI is low,³³ making the risk of systemic immunosuppression with TCIs not biologically plausible.^{39,40} In Hui et al's study³² and Schneeweiss et al's study,²² the low level of exposure to TCIs before lymphoma occurrence—amounting to only 2 to 3 tubes of topical preparation—does not support a causal association between TCI and lymphoma. However, the significant association between tacrolimus and lymphoma in the study by Hui et al³² deserves additional follow-up. The hypothesis of a confounding factor of CTCL misdiagnosed as AD and treated with tacrolimus needs to be further substantiated.

One potential limitation of this meta-analysis is that the role of systemic immunosuppressant medications, such as azathioprine, cyclosporine, or phototherapy, could not be assessed. The information about the use of these agents was not available from these publications.

In conclusion, there is a modest increased risk of lymphoma in patients with severe AD. TCIs and TCSs do not appear to significantly contribute to the overall risk. Misdiagnosis of CTCL as AD is an important point that deserves clinician awareness.

It may in part drive the association between severe AD and lymphoma.

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