

Lymphoma among patients with atopic dermatitis and/or treated with topical immunosuppressants in the United Kingdom

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Background: Atopic dermatitis (AD) has been associated with an increased risk of lymphoma.

Objectives: To assess the risk of lymphoma associated with AD and use of topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) in a database allowing medical record validation.

Methods: We conducted a nested-case control study using the United Kingdom-based The Health Improvement Network (THIN) database. We excluded patients with established risk factors for lymphoma. Cases of lymphoma were identified and classified after review of the medical records and hospital discharge files.

Results: In the study population of 3,500,194 individuals, we identified 2738 cases of lymphoma (1722 non-Hodgkin lymphoma [NHL], 466 Hodgkin disease, 550 indeterminate cases; overall, 188 had cutaneous involvement) and 10,949 matched controls. AD was associated with an increased lymphoma risk (odds ratio [OR], 1.83; 95% CI, 1.41-2.36). In patients with AD referred to a dermatologist, the OR further increased (OR, 3.72; 95% CI, 1.40-9.87). We did not find any cases of lymphoma in TCI users; however, the number of patients exposed to TCI was insufficient to study any possible association between lymphoma and these drugs. TCS use was associated with an increased lymphoma risk (OR, 1.46; 95% CI, 1.33-1.61). The risk increase was dependent on TCS potency (OR for high-potency TCS, 1.80; 95% CI, 1.54-2.11). The increased risk involved both Hodgkin disease and NHL, especially NHL with skin involvement (OR for high-potency TCS, 26.24; 95% CI, 13.49-51.07).

Conclusion: Our results show an association between lymphoma—especially skin lymphoma—and use of TCS. The risk increased with duration of exposure and potency of TCS. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Lymphoma, skin lymphoma, topical corticosteroids, atopic dermatitis, risk

Söderberg et al¹ found an association between childhood eczema and non-Hodgkin lymphoma (NHL) in adulthood (relative risk, 2.3; 95% CI, 1.0-5.3). Zhang et al² found an increased odds ratio (OR) of T-cell NHL among patients with eczema (OR, 2.5; 95% CI, 1.1-5.7). Some studies have reported an increased risk of lymphoma in atopic dermatitis (AD),³ whereas others have shown inconclusive results or even a decrease in risk of lymphoma.⁴ A recent observational study in US patients with AD showed that increasing age, use of oral corticosteroids, and severe AD were associated with an increased risk of lymphoma. Use of high-potency topical corticosteroids (TCS) was associated with a slight increase in lymphoma risk. However, this result was compatible with a chance finding, and the diagnosis of lymphoma could not be validated with medical records.⁵

Systemic, continuous use of immunosuppressive agents increases the risk of lymphoma,⁶ usually after some secondary stimulus like a viral infection with EBV or other viruses.^{7,8} There have been isolated reports of lymphoma in patients treated with topical calcineurin inhibitors (TCI).⁹

We undertook this nested case-control study to assess further the risk of lymphoma associated with the use of TCI and TCS and its relation with severity of AD in a source population in which the diagnosis of lymphoma can be validated.

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METHODS

Source population and data

We conducted the study in The Health Improvement Network (THIN) database, which is representative of the United Kingdom general population. The THIN dataset contains data from 314 medical practices with more than 5.5 million patients (<http://www.thin-uk.com>).

Study population

We identified patients of all ages with at least 6 months of enrollment in a THIN-registered practice between January 1, 1992, and March 23, 2006. Then we excluded patients >79 years of age at cohort entry and those with a diagnosis of established risk factors for lymphoma (previous diagnosis of lymphoma, cancer, immunosuppression, transplantation, HIV infection/

Abbreviations used

AD: Atopic dermatitis
 GP: General practitioner
 HD: Hodgkin disease
 NHL: Non-Hodgkin lymphoma
 OR: Odds ratio
 TCI: Topical calcineurin inhibitor
 TCS: Topical corticosteroid
 THIN: The Health Improvement Network

AIDS, psoriasis, rheumatoid arthritis, SLE, Sjögren syndrome, celiac sprue, and those patients with prescriptions for immunosuppressive agents and anticancer drugs) before the cohort entry date.

Cohort definition

Within the general cohort, we defined exposed patients as those with at least 1 prescription for TCS, pimecrolimus, and/or tacrolimus during the study period. Patients without any TCS or TCI prescription were considered unexposed. Patients with a history of AD were identified by READ codes M11.00, M11.z and M111-117. Patients with an AD diagnosis referred to a dermatologist were considered to have severe AD.

Cohort follow-up

Patients were followed up from either January 1, 1992, or the time of a prescription of a TCI or TCS to earliest of becoming a case, developing any exclusion criterion (see study population), turning older than 79 years, death, or March 23, 2006.

Case identification and characterization

Cases of lymphoma were identified by the presence of a READ code for lymphoma in the medical records of patients after the cohort entry date. Cases of lymphoma were first identified from a list of codes by 2 investigators (F.M.A. and E.C.) blind to exposure. Of this initial list, cases of adenolymphoma (benign tumor of the salivary glands¹⁰) were excluded. Lymphoma cases were classified following the World Health Organization (WHO) classification.¹¹ Skin lymphomas were classified—when possible—according to the WHO-European Organization for Research and Treatment of Cancer classification.¹²

Case validation

When record review did not allow classification of lymphoma into Hodgkin disease (HD) or NHL, we solicited a review of actual medical records. Review was also solicited for all cases with suspected skin involvement. The validation process included a questionnaire sent to the general practitioner, and review of the medical records and hospital discharge files.

Selection of controls

The case-control design can be conceptualized as a follow-up design in which the person-time experience of the denominators of the incidence rate is sampled rather than measured outright. Controls are a sample of the combined cohorts that gave rise to the cases, and a control can be chosen for more than 1 case. We matched potential controls to cases by age (± 5 years) at index date (date of lymphoma diagnosis in the medical record), sex, and practice, and then randomly selected 4 controls for each case. The end of follow-up for the controls was defined as the date the corresponding case was diagnosed with lymphoma (risk-set control sampling).

For the analysis performed within the AD population and non-AD population, 2 additional sets of controls were selected in the same way, 1 among the AD subcohort and another among the non-AD cohort.

Exposure to medications

We defined the exposure to the study drugs of interest as follows:

1. TCS: We classified the potency according to a modified version of the US National Psoriasis Foundation (<http://www.psoriasis.org/treatment/psoriasis/steroids/potency.php>). This classification grades TCS potency from grade 1 (super potent) to grade 7 (least potent). We limited the analysis to high potent TCS (class 1-2; see this article's Table E1 in the Online Repository at www.jacionline.org) versus all others (3-7). Exposure to TCI and TCS was estimated by creating a course of therapy for each exposed patient. Cases and controls were allocated to 1 of 5 mutually exclusive exposure groups depending on the drugs used between the cohort entry date and the development of lymphoma or a patient being chosen as a control:
 - a. TCS: if there was a prescription for a TCS but not for a TCI. A patient who may have received both a high-potency and low-potency TCS at some point in time was classified only as high-potency TCS user.
 - b. Pimecrolimus: if there was a prescription for pimecrolimus regardless of the presence of a prescription for TCS.
 - c. Tacrolimus: if there was a prescription for tacrolimus regardless of the presence of a prescription for TCS.
 - d. Both (tacrolimus and pimecrolimus): if there was a prescription for pimecrolimus and tacrolimus regardless of the presence of a prescription for TCS.
 - e. No exposure with a study drug of interest: absence of prescription recorded for any TCS or TCI.
2. Duration of exposure. We created a proxy for the length of exposure by dividing the prescription quantity by the amount prescribed per day. Patients were then classified into 5 categories (<30 days, 30 days to 6 months, 6 months to 1 year, 1-2 years, and >2 years). Patients were classified as 1-course users if they were covered by a prescription less than 31 days of treatment. If they had 31 days or more covered by treatment, we identified the period covered by treatment.

Analyses

The relationship among exposure to medications, severity of the disease, and the occurrence of lymphoma was described in cross-tabulations. To assess the relationship between exposure and lymphoma (expressed as OR, 95% CI), we used a conditional (fixed effects) logistic regression model. In addition to matching on age, sex, and practice, potential confounders (Table I) were controlled for using a backward elimination process—that is, by stepwise deletion of the confounder that made the smallest change in the exposure effect estimate on deletion, provided that the effect of the confounder was $\leq 10\%$ of the estimated effect. Any confounder with an effect $>10\%$ on the estimate and confidence limits accrued from the start of the process was kept in the model.

All analyses were conducted by using SAS version 9.1 (SAS Institute Inc, Cary, NC) and STATA version 7.0 (StataCorp LP, College Station, Tex).

RESULTS**Study of the determinants of lymphoma**

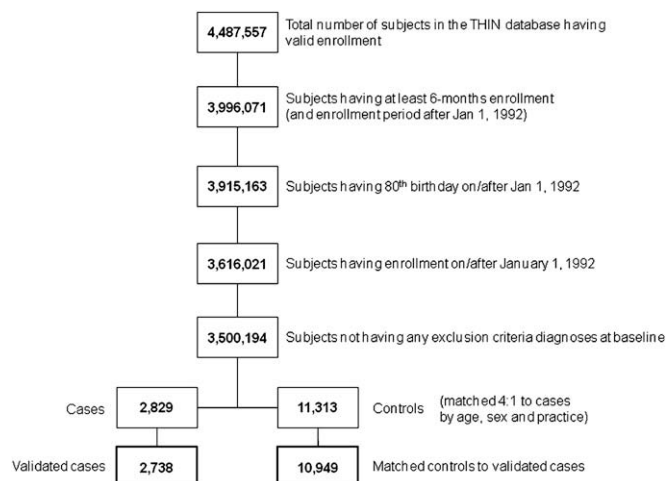
Fig 1 shows a flowchart describing the process of patient selection. After applying exclusion criteria, the cohort included 3,500,194 persons. Approximately 5% had AD. Less than 1% of patients were coded as being infected by EBV.

At cohort entry, there were 204,613 (6% of the overall cohort) users of TCS (86% were users of lower-potency TCS). There were only a few users of pimecrolimus ($n = 113$) and tacrolimus ($n = 133$).

Hydrocortisone alone or in combination was the most frequently prescribed TCS overall and low-potency TCS. Clobetasol was the most frequently prescribed high-potency TCS (Table E1). Indications for drug prescriptions are not included in THIN, so we looked for disease codes within 30 days before or after a TCS

TABLE I. Demographic characteristics of the lymphoma cases and controls

Total	No. of cases	%	No. of controls	%
Age (y)	2,738	100	10,949	100
0-2	25	1	87	1
3-5	14	<1	71	1
6-10	25	1	142	1
11-20	109	4	367	3
21-30	186	7	818	7
31-40	326	12	1,287	12
41-50	514	19	2,090	19
51-60	674	25	2,655	24
61+	865	32	3,432	31
Sex				
Male	1,547	57	6,188	57
Female	1,191	43	4,761	43
Presence of EBV				
Anytime in baseline	21	1	43	<1
In follow-up period	9	<1	6	<1
Anytime in baseline or follow-up	30	1	49	<1
Presence of asthma as comorbidity				
Anytime in baseline or follow-up	307	11	1,043	9
Presence of AD				
No	2,644	97	10,742	98
AD cared for by GP only	83	3	197	2
AD cared for by specialist	11	<1	10	<1

**FIG 1.** Description of patient selection for occurrence of lymphoma among patients with atopic dermatitis and/or treated with topical immunosuppressants in the United Kingdom.

prescription. We did not find any evidence of the presence of diagnoses compatible with the exclusion criteria.

Validation of lymphoma cases

We initially identified 2829 cases in the electronic records. Validation of diagnosis was sought for 1274 cases. THIN practices agreed to submit information for 842 (66%). By the end of the validation timeline, we received information for 760. Of these, 18 forms were invalid because of lack of information. Of the remaining 742, the diagnosis was confirmed in 684; thus, the positive predictive value of the diagnosis of lymphoma was 92%.

TABLE II. Risk of lymphoma associated with topical corticosteroid (stratified by potency) and topical calcineurin inhibitor use

Medications	Cases N = 2,738	Controls N = 10,949	Adjusted*	
			OR	95% CI
Nonuse	1,812	8,147	Reference	
TCS	926	2,799	1.46	1.33-1.61
High potency	283	672	1.80	1.54-2.11
Low potency	641	2,117	1.36	1.22-1.51
Pimecrolimus	0	0		
Tacrolimus	0	3		
Pimecrolimus + tacrolimus	0	0		

*Controls matched for sex, age, and practice; model adjusted for presence of infectious mononucleosis, asthma diagnosis, oral corticosteroid use, AD diagnosis, and severity of AD.

TABLE III. Risk of lymphoma associated with topical corticosteroid use stratified by potency and duration of exposure

Medications	Cases N = 2,738†	Controls N = 10,949†	Adjusted*	
			OR	95% CI
Nonuse of TCS	1,812	8,147	Reference	
Low potency				
<30 d	318	1,079	1.34	1.16-1.54
30 d to 6 mo	262	827	1.42	1.22-1.66
6 mo to 1 y	34	124	1.23	0.83-1.80
1-2 y	19	57	1.49	0.88-2.52
More than 2 y	8	30	1.16	0.53-2.54
High potency				
<30 d	48	167	1.3	0.94-1.81
30 d to 6 mo	149	343	1.88	1.53-2.31
6 mo to 1 y	37	90	1.70	1.14-2.53
1-2 y	32	53	2.52	1.59-4.01
>2 y	17	22	3.21	1.67-6.17

*Controls matched for sex, age, and practice; model adjusted for presence of infectious mononucleosis, asthma diagnosis, oral corticosteroid use, AD diagnosis, and severity of AD.

†There were 12 subjects with missing TCS potency information (2 cases and 10 controls).

After the validation process, there were 2738 cases of lymphoma. Of these, 1722 were NHL, 466 HD, and 550 indeterminate cases. Among the NHL cases, 367 were B-cell NHL (NHL-B) and 52 T-cell NHL (NHL-T). Overall, 188 cases had cutaneous involvement; all of them were NHL except 1 classified as indeterminate.

Characteristics of cases and controls

Table I shows the demographics of the 2738 cases and the 10,949 matched controls (there were no unmatched cases). The association between lymphoma and EBV infection was increased, but the one with asthma was not (data not shown). AD was associated with an increased risk of lymphoma (OR, 1.83; 95% CI, 1.41-2.36; all ORs adjusted unless otherwise specified). Severe AD further increased the risk of lymphoma (OR, 3.72; 95% CI, 1.40-9.87).

Table II shows the cross-tabulations of the association between lymphoma and topical immunosuppressant use. We did not find any case of lymphoma in TCI users, but the number of patients exposed to TCI was insufficient to study any possible association between lymphoma and these drugs. The use of TCS was

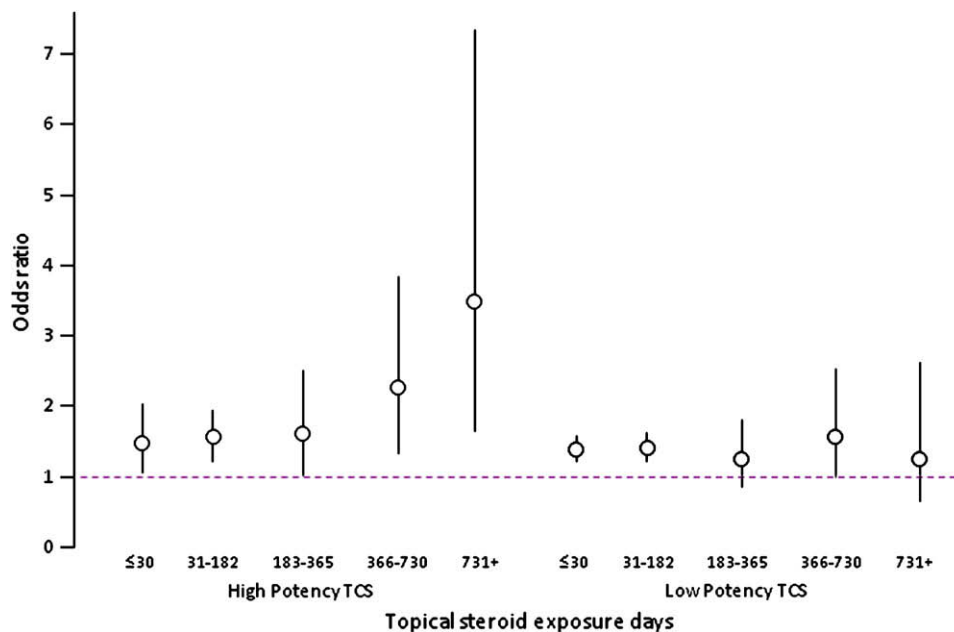


FIG 2. Risk of lymphoma associated with duration of exposure to TCS, stratified by TCS potency, ignoring the 12 months before case date.

TABLE IV. Risk of NHL with skin involvement associated with TCSs stratified by duration of exposure

Medications	Cases N = 188	Controls N = 752	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use of TCS	66	574				
<30 d	28	85	3.95	2.29-6.80	3.85	2.22-6.66
30 d to 6 mo	65	70	15.76	8.91-27.9	14.83	8.28-26.58
6 mo to 1 y	14	10	27.34	10.28-72.68	25.75	9.51-69.69
1-2 y	8	11	13.77	4.44-42.73	12.92	3.99-41.89
>2 y	7	2	83.04	9.36-736.9	82.91	9.29-740.2

*Controls matched for sex, age, and practice; model adjusted for presence of infectious mononucleosis, asthma diagnosis, oral corticosteroid use, AD diagnosis, and severity of AD.

associated with an increased risk of lymphoma (OR, 1.46; 95% CI, 1.33-1.61). The risk increase was more pronounced among high-potency TCS users and was apparent soon after starting treatment with TCS. In users of high-potency TCS, the association became stronger with increasing duration of exposure, whereas the association could not be observed in patients treated with low-potency TCS (Table III; Fig 2).

In patients with AD, the OR for users of high-potency TCS was 4.93 (95% CI, 2.28-10.63) (Table E2), whereas in patients without AD, the OR was 1.92 (95% CI, 1.64-2.27) (Table E3). For low-potency TCS, the OR was 3.07 (95% CI, 1.55-6.06) in patients with and 1.43 (95% CI, 1.28-1.59) in patients without AD. Stratification by lymphoma type yielded differing results. For the approximately 20% of cases that remained indeterminate after the validation process, the ORs were compatible with no effect, and we found no evidence of a potency or duration of use effect.

Compared with non use, in patients with NHL, exposure to TCS was associated with an increased lymphoma risk that was potency-dependent (OR, 1.96; 95% CI, 1.62-2.37 for high-potency TCS). The risk also increased with duration of exposure (see this article's Tables E4 and E5 the Online Repository at

www.jacionline.org). Because the number of cases that could be subclassified into NHL-B and NHL-T was relatively low, this subanalysis yielded results with wider CIs. However, the potency effect was still evident; the effect of duration showed a trend but with low precision (see this article's Tables E6, E7, E8 and E9 in the Online Repository at www.jacionline.org). We also found an association of use of TCS with an increase in risk of HD that was potency-dependent (OR for high-potency TCS, 2.14; 95% CI, 1.43-3.21). The risk also increased with increasing duration of exposure (see this article's Tables E10 and E11 in the Online Repository at www.jacionline.org).

The use of TCS was associated with a high risk of NHL with skin involvement. The OR for users of low-potency TCS was 5.35 (95% CI, 3.34-8.57), whereas the risk for high-potency TCS users was 26.24 (95% CI, 13.49-51.07). Duration of TCS exposure also showed a strong association with the risk of lymphoma with skin involvement (Table IV; see this article's Tables E12 and E13 in the Online Repository at www.jacionline.org). ORs ranged from 3.85 (95% CI, 2.22-6.66) in users with less than 30 days of exposure to 82.91 (95% CI, 9.29-740) in users with more than 2 years of TCS exposure.

DISCUSSION

Our results show an increased risk of lymphoma in patients receiving TCS. The risk increased with use of high-potency TCS and with longer duration of exposure. The risk increase was seen in HD, NHL, and, especially, cases of NHL with skin involvement. We did not find any cases of lymphoma in TCI users, but exposure was insufficient to study the risk of lymphoma associated with their use.

The strength of the association, especially for the cases of skin lymphoma, the potency, and the temporal relationship with exposure duration support a causal relationship between TCS exposure and lymphoma. However, part of the association we observed is probably a result of confounding by indication. A precancerous stage presenting with chronic cutaneous inflammatory features is common in cutaneous T-cell lymphomas, which can take years from the time of initial presentation to diagnosis^{13,14} and maybe treated with high-potency TCS.^{15,16} Although confounding by indication may explain some of the observed effect, it is unlikely to be the only explanation. It is difficult to accept that an OR as high as 82.91 (skin lymphoma in users >2 years) would have confounding by indication as the only explanation. Confounding by indication also may not explain why oral corticosteroids were a risk factor for lymphoma in the study population, a finding previously described.⁹ Nor would it explain the association between HD and TCS because skin involvement in HD is rare.¹⁷

It is implausible that a lymphoma would be caused by a short exposure to TCS (or most drugs). Thus, we show the results considering 12 months as the minimum induction period for lymphoma (Fig 2). The risk of lymphoma increased with longer exposure to high-potency, but not low-potency, TCS. The results were unchanged when repeating the analysis considering 6 months as the minimum induction period for lymphoma (data not shown).

The use of systemic corticosteroids has been associated with an increased risk of NHL in various studies,¹⁸⁻²¹ although others did not show such an increase.^{22,23} Zhang et al² reported an increased OR (1.5; 95% CI, 0.8-2.9) for NHL in women using steroid anti-inflammatory drugs. The increase was seen only in patients with a long duration of use (OR, 2.6; 95% CI, 1.1-6.1). Chang et al²⁴ reported no increase in the overall risk of lymphomas with systemic corticosteroids, but they found an increased risk of T-cell NHL. A recent meta-analysis of epidemiologic studies showed no increased lymphoma risk in association with systemic corticosteroid use.²⁵ The authors of this meta-analysis argued that those studies showing an increased risk of lymphoma with oral corticosteroids might be confounded by indication—that is, many diseases for which oral corticosteroids were indicated are *per se* associated with an increased risk of lymphoma.²⁶ We excluded patients with conditions known to carry an increased risk of lymphoma (eg, rheumatoid arthritis, lupus, psoriasis) or that may be associated with use of systemic immunosuppressants (eg, cancer, transplantation). So, although a meta-analysis may not be able to differentiate the effect of systemic corticosteroids when intermingled with that of other causes of lymphoma, it is possible that by excluding patients with established risk factors for lymphoma, the effect became apparent.

Whatever the mechanism, the risk may be expected to increase with stronger TCS potency or prolonged use. In our study, the relationship with increasing duration of use

observed is circumscribed to patients receiving high-potency TCS. However, in patients with skin NHL, both low-potency and high-potency TCS were associated with an increased risk of lymphoma, although the risk increase in high-potency users was more pronounced.

Atopic dermatitis has been described to increase the risk of lymphoma.³ TCS increased the risk of lymphoma in a potency-dependent manner in patients with and without AD, but the risk increase was higher in patients with AD than in patients without (see this article's Tables E2 and E3 in the Online Repository at www.jacionline.org). Furthermore, patients with severe AD (ie, those referred to a dermatologist) had an increased risk of lymphoma compared with patients without AD, but also compared with patients with less severe AD (ie, those not referred to a dermatologist). We found use of oral corticosteroids to be associated with an increased lymphoma risk in patients without AD but not with AD, which suggests that there may be an uneven distribution of oral corticosteroid users among TCS users.

Length of exposure to topical agents was estimated from prescription data. Therefore, our approach can only be considered an approximation of exposure duration. To confirm our results on exposure, further studies are necessary. Also, the measurement of exposure to TCS in this study was limited to potency of TCS and duration of exposure, not the cumulative amount of TCS used. In addition, actual drug use (ie, compliance with the prescribed dosage, dosage schedule, and so forth) cannot be verified. However, compliance can be expected to increase with longer follow-up because it is unlikely that a patient would receive prescriptions for months and then not apply the prescribed topical treatment. Compliance may also differ between patients exposed to high-potency and lower-potency TCS. If this would result in a bias, it would underestimate the risk associated with high-potency TCS because a patient who may have received both a high-potency and a low-potency TCS at some point was classified only as a high-potency TCS user. Information on the indication for TCS use was not readily available; consequently, it is not possible to know with certainty for what underlying skin conditions the TCSs were in fact prescribed. Finally, information on over-the-counter drug use is lacking in THIN. The effect of missing over-the-counter drug use in epidemiologic research has been considered negligible in other studies.²⁷

This study bears some similarities to a previous one we conducted based on data from a US health care database. In that study too, severe AD and use of oral corticosteroids increased the risk of lymphoma. The current study yielded a clearly increased risk of lymphoma in patients receiving high-potency TCS, whereas the US study showed only a slightly increased risk compatible with a chance finding. It is difficult to compare these 2 studies, because the 2 databases represent different populations, data sources (administrative data vs primary care medical records), and health systems. Furthermore, the US database did not allow medical record validation.

In conclusion, our results show an association between lymphoma and use of TCS, especially for skin lymphoma. Although the relative risk of skin lymphoma was high, the absolute risk was low (188 cases/22,811,265 person-years of exposure = 8.2 cases/million patient-years). The risk increased with duration of exposure and potency of TCS. A patient's individual risk may be determined by the presence of AD, its severity, and the use and type of TCS and oral corticosteroids.

Clinical implications: Patients' individual risk of lymphoma with TCS use is determined by the presence of AD, its severity, and the duration and potency of TCS and oral corticosteroids. However, the absolute risk is low, and results need confirmation.

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TABLE E1. List of topical steroids potency 1-2*

Clobetasol propionate 0.05%
Diflorasone diacetate 0.05%
Halobetasol propionate 0.05%
Amcinonide 0.1%
Augmented betamethasone dipropionate 0.05%
Betamethasone dipropionate 1%
Desoximetasone 0.25%
Fluocinonide 0.05%
Halcinonide 0.1%
Mometasone furoate 0.1%

*When a concentration is listed, compounds with the concentration listed or greater were included.

TABLE E2. Risk of lymphoma (OR, 95% CI) associated with topical steroid use in patients with AD stratified by topical steroid potency

Medications	Cases N = 94	Controls N = 371†	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use	15	130				
Topical corticosteroid (high potency)	37	89	4.99	2.36-10.57	4.93	2.28-10.63
Topical corticosteroid (low potency)	42	151	2.97	1.51-5.87	3.07	1.55-6.06
Asthma	23	79			1.92	0.87-4.25
Severe AD	11	12			3.72	1.40-9.87
Oral steroids	23	90			0.55	0.25-1.22

*Controls matched for sex, age, and practice; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, oral steroid use, and severity of AD.

†There was 1 control with missing TCS potency information.

TABLE E3. Risk of lymphoma (OR, 95% CI) associated with topical steroid use in patients without AD stratified by topical steroid potency

Medications	Cases N = 2,644	Controls N = 10,573 [†]	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use	1,797	8,075				
Topical corticosteroid (high potency)	246	579	2.01	1.71-2.36	1.92	1.64-2.27
Topical corticosteroid (low potency)	599	1,913	1.47	1.32-1.64	1.43	1.28-1.59
Asthma	272	898			0.90	0.76-1.07
Oral steroids	527	1,493			1.53	1.34-1.75

*Controls matched for sex, age, and practice; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, and oral steroid use.

[†]There were 2 cases and 6 controls with missing TCS potency information.

TABLE E4. Risk of NHL (OR, 95% CI) associated with topical steroids and stratified by topical steroid potency

Medications	Cases N = 1722	Controls N = 6885 [†]	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use of TCS	1089	4997				
Topical corticosteroid (high potency)	198	452	2.1	1.74-2.52	1.96	1.62-2.37
Topical corticosteroid (low potency)	433	1427	1.45	1.27-1.65	1.41	1.24-1.62

*Controls matched for sex, age, and practice; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, oral steroid use, AD diagnosis, and severity of AD.

[†]There were 2 cases and 9 controls with missing TCS potency information.

TABLE E5. Risk of NHL (OR, 95% CI) associated with topical steroids and stratified by duration of exposure

Medications	Cases N = 1722	Controls N = 6885	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use of TCS	1089	4997				
<30 d	246	807	1.44	1.23-1.69	1.42	1.21-1.67
30 d to 6 mo	280	800	1.69	1.44-1.98	1.62	1.38-1.9
6 mo to 1 y	55	159	1.68	1.29-2.31	1.55	1.13-2.14
1-2 y	34	84	2	1.32-3.01	1.84	1.21-2.8
>2 y	18	38	2.31	1.31-4.08	2.12	1.2-3.76

*Controls matched for sex, age, and practice; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, oral steroid use, AD diagnosis, and severity of AD.

TABLE E6. Risk of NHL-B (OR, 95% CI) associated with topical steroids and stratified by topical steroid potency

Medications	Cases N = 367	Controls N = 1465	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use of TCS	251	1087				
Topical corticosteroid (high potency)	33	79	1.83	1.18-2.83	1.84	1.18-2.88
Topical corticosteroid (low potency)	83	299	1.23	0.92-1.64	1.23	0.92-1.63

*Controls matched for sex, age, and practice; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, oral steroid use, AD diagnosis, and severity of AD.

TABLE E7. Risk of NHL-B (OR, 95% CI) associated with topical steroids and stratified by duration of exposure

Medications	Cases N = 367	Controls N = 1465	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use of TCS	251	1087				
<30 d	47	175	1.19	0.84-1.69	1.18	0.83-1.68
30 d to 6 mo	52	146	1.58	1.10-2.27	1.58	1.10-2.27
6 mo to 1 y	13	30	1.92	0.98-3.74	1.92	0.98-3.77
1-2 y	4	15	1.17	0.39-3.55	1.20	0.38-3.72
>2 y	0	12	0	0-INF	0	0-INF

*Controls matched for sex, age, and practice; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, oral steroid use, AD diagnosis, and severity of AD.

TABLE E8. Risk of NHL-T (OR, 95% CI) associated with topical steroids and stratified by topical steroid potency

Medications	Cases N = 52	Controls N = 208	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use of TCS	32	150				
Topical corticosteroid (high potency)	6	12	2.44	0.83-7.16	3.10	0.94-10.27
Topical corticosteroid (low potency)	14	46	1.50	0.70-3.21	1.42	0.65-3.12

*Controls matched for sex, age, and practice; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, oral steroid use, AD diagnosis, and severity of AD.

TABLE E9. Risk of NHL-T (OR, 95% CI) associated with topical steroids and stratified by duration of exposure

Medications	Cases N = 52	Controls N = 208	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use of TCS	32	150				
<30 d	7	20	1.69	0.64-4.47	1.64	0.61-4.39
30 d to 6 mo	11	30	1.87	0.80-4.40	1.91	0.79-4.62
6 mo to 1 y	0	6	0	0-INF	0	0-INF
1-2 y	2	2	4.83	0.66-35.27	6.04	0.67-54.89
>2 y	0	0	—	— —	—	— —

*Controls matched for sex, age, and practice; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, oral steroid use, AD diagnosis, and severity of AD.

TABLE E10. Risk of HD (OR, 95% CI) associated with topical steroids and stratified by topical steroid potency

Medications	Cases N = 466	Controls N = 1,864 [†]	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use of TCS	327	1487				
Topical corticosteroid (high potency)	46	90	2.44	1.66-3.58	2.14	1.43-3.21
Topical corticosteroid (low potency)	93	285	1.55	1.18-2.05	1.42	1.08-1.89

*Controls matched for sex, age, and practice ; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, oral steroid use, AD diagnosis, and severity of AD.

[†]There were 2 controls with missing TCS potency information.

TABLE E11. Risk of HD (OR, 95% CI) associated with topical steroids and stratified by duration of exposure

Medications	Cases N = 466	Controls N = 1,864	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use of TCS	327	1487				
<30 d	55	197	1.32	0.95-1.84	1.25	0.90-1.75
30 d to 6 mo	63	144	2.14	1.53-2.99	1.93	1.37-2.73
6 mo to 1 y	9	20	2.33	1.03-5.31	1.91	0.82-4.47
1-2 y	8	14	2.66	1.11-6.38	2.20	0.89-5.45
>2 y	4	2	10.60	1.92-58.60	9.65	1.68-55.57

*Controls matched for sex, age, and practice; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, oral steroid use, AD diagnosis, and severity of AD.

TABLE E12. Risk of NHL with skin involvement (OR, 95% CI) associated with topical steroids and stratified by topical steroid potency

Medications	Cases N = 188	Controls N = 752	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use of TCS	66	574				
Topical corticosteroid (high potency)	58	35	27.21	14.18-52.24	26.24	13.49-51.07
Topical corticosteroid (low potency)	64	143	5.67	3.56-9.01	5.35	3.34-8.57

*Controls matched for sex, age, and practice; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, oral steroid use, AD diagnosis, and severity of AD.

TABLE E13. Risk of NHL with skin involvement (OR, 95% CI) associated with topical steroids and stratified by duration of exposure

Medications	Cases N = 188	Controls N = 752	Unadjusted		Adjusted*	
			OR	95% CI	OR	95% CI
Non use of TCS	66	574				
<30 d	28	85	3.95	2.29-6.80	3.85	2.22-6.66
30 d to 6 mo	65	70	15.76	8.91-27.90	14.83	8.28-26.58
6 mo to 1 y	14	10	27.34	10.28-72.68	25.75	9.51-69.69
1-2 y	8	11	13.77	4.44-42.73	12.92	3.99-41.89
>2 y	7	2	83.04	9.36-736.94	82.91	9.29-740.17

*Controls matched for sex, age, and practice; model adjusted for sex, age, presence of infectious mononucleosis, asthma diagnosis, oral steroid use, AD diagnosis, and severity of AD.