Long-term topical corticosteroid use and risk of skin cancer: a systematic review protocol

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Review question/objective: The objective of this systematic review is to synthesize the best available research evidence to determine the risk of skin cancer in patients on long-term use of topical corticosteroids. Specifically the review question is: In people using long-term (regular use over one month) topical corticosteroids, what is the risk of developing skin cancer (clinically or histologically confirmed basal cell carcinoma, squamous cell carcinoma or melanoma)?

Keywords Basal cell carcinoma; keratinocyte; melanoma; non-melanoma; topical corticosteroids

Background

Topical corticosteroids (TCS) are used to reduce inflammation and are one of the most commonly prescribed medicines in dermatology. They were first used successfully by Sulzberger and Witten in 1952, and their success marked a cornerstone in the history of dermatology.1 Topical corticosteroids are the mainstay of atopic dermatitis treatment and used for other skin conditions such as psoriasis, where they are often required for months or years to control the disease and ultimately restore patients’ quality of life. Numerous TCS are now available in different preparations, concentrations and potencies; however, when used appropriately, TCS efficacy and safety are well established.2-6

The beneficial anti-inflammatory effects of TCS are complex, being largely mediated via the cytoplasmic steroid receptor and involving actions on circulating cellular and cytokine mediators of inflammation as well as on the peripheral vasculature.7 The use of TCS is tempered by consideration of local and less frequently encountered systemic side effects. Known local side effects include skin atrophy, contact allergy, acne, mild hypopigmentation and hypertrichosis. Rarely, absorption through the skin can cause adrenal suppression. The risk of developing side effects is related to the potency, preparation, frequency and duration of use and the age of the patient. In clinical practice, these side effects are uncommon when TCS are used within their guidance.

There are two types of skin cancers: melanoma skin cancer and non-melanoma skin cancer (NMSC) (keratinocyte). Around 97% of NMSC comprise mainly of basal cell carcinomas (BCCs) or cutaneous cell carcinomas. The incidence of NMSC is increasing worldwide,8-12 with an estimated two to three million new cases of NMSC recorded each year.13 With respect to cutaneous malignant melanoma (CMM), this is the most serious form of skin cancer and has been increasing steadily in incidence over the past 30 years.14 Mortality due to CMM is much higher than that of NMSC.15

There are several observational studies that have looked at the relative risk of developing skin cancer due to oral corticosteroid exposure.16,17 These studies have provided conflicting results as to whether corticosteroids are associated with an increased risk of skin cancer. Karagas et al.16 conducted a case-control study on over 800 non-transplant squamous cell carcinoma (SCC) and BCC patients. The authors found that oral glucocorticoids may increase the risk of NMSC, whereas Baibergenova et al.17 found no association between NMSC and oral corticosteroids in a follow-up study of a chemotherapy trial with 1051 study participants. These studies highlight the clinical equipoise that exists.
around the impact oral corticosteroids have on the risk of skin cancer.

There have been several epidemiological studies that have explored the risk of cancer specifically among atopic dermatitis patients. Hagstroemer et al.\(^{18}\) conducted a hospital-based study on 15,666 patients with atopic dermatitis in Sweden between 1965 and 1999.\(^{18}\) The authors reported that men faced a 50% increased risk of NMSC during the first 10 years of follow-up, but this did not reach statistical significance. Wang and Diepgen\(^{19}\) conducted a review of atopic dermatitis studies published before 2004, and no consistent associations were observed for skin cancers. This review did not look at the effect of TCS use on the risk of skin cancer. At present, we do not know in particular what impact TCS have on the risk of skin cancer in the atopic dermatitis population.

With regard to the organ transplant population, it is well established that immunosuppression increases the risk of skin malignancy.\(^{20,21}\) This occurs when systemic corticosteroids are used, although most studies include patients treated with a combination of immunosuppressants including azathioprine and calcineurin inhibitors.\(^{22,23}\) Corticosteroids are known to have an immunosuppressive effect, and TCS may have a local immunosuppressive effect. It is not known whether TCS may increase the risk of skin cancer through this mechanism.

On the other hand, it is possible that treating skin inflammation with TCS may reduce the risk of skin cancer. Several systematic reviews and meta-analyses report the benefits of anti-inflammatory drugs in reducing the risk of cancer, including skin cancers.\(^{24,25}\) The management of certain types of inflammatory skin diseases includes the rationale that reducing inflammation reduces the risk of SCC development in vulval and penile lichen sclerosus as well as hypertrophic lichen planus. It is also known that chronic inflammation is a risk for the development of SCC, such as in chronic ulceration and the development Marjolin’s ulcer.\(^{26,27}\) This mainly holds true for SCC but less is known about BCC and melanoma. Therefore, overall TCS may decrease the risk of skin cancer in patients in whom TCS are used to treat inflammatory skin disease.

A search of MEDLINE and Embase revealed that no published systematic reviews or meta-analyses have been performed to collate evidence on long-term TCS use on the risk of skin cancer. Immunosuppression induced by TCS, either local or systemic, may allow these cancers to emerge from reduced innate immunosurveillance. However, TCS may also reduce the risk of skin cancer in patients in whom TCS are used to treat inflammatory skin disease. With TCS use being one of the most commonly prescribed drugs in the clinical field of dermatology and the increasing incidence of skin cancer, there is a need to review all current evidence about the possible association.

**Inclusion criteria**

**Types of participants**
The current review will consider studies that include people of all ages, genders and ethnicities.

Participants with HIV, transplant participants or participants with genetic diseases (e.g. Gorlin–Goltz syndrome) will be included.

**Exposure of interest**
The current review will consider studies that evaluate long-term use of TCS. Our definition of “long-term” consists of more than once a week for a month or longer.

**Outcomes**
The current review will consider studies that include the following outcome measures: non-melanoma skin cancer, cutaneous SCC, BCC or melanoma skin cancer. These outcomes will be measured by a clinical diagnosis and, where available, histological confirmation. Studies looking at the outcomes in oral, vulvar or genital sites only will not be included as these are not relevant in the context of our hypothesis. Precursors such as Bowen’s disease will be secondary outcomes.

**Types of studies**
The current review will include analytical comparative observational studies including prospective and retrospective cohort studies, case-control studies and cross-sectional studies.

**Search strategy**
The search strategy will aim to identify both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and Embase will be undertaken followed by an analysis of the text words
contained in the title and abstract, and of the index terms used to describe the article. A second search using identified keywords and index terms has been used to develop a comprehensive search strategy. The search strategy for MEDLINE is detailed in Appendix I. Third, the reference list of all identified reports and articles will be searched for additional studies. Studies published in all languages will be included. There will be no date exclusion.

Information sources
The electronic databases to be searched include: MEDLINE, Embase and LILACS all from inception to current date.

The search for unpublished studies will include: skin cancer experts who have been identified from the included studies will be contacted. We will also search EThOS at the British library (http://ethos.bl.uk) to identify other unpublished work.

Study selection
Following the search, all identified citations will be collated and uploaded in EndNote and duplicates removed. Titles and abstracts will then be screened by two independent reviewers (SR and EBT) for assessment against the inclusion criteria for the review. Studies that appear to meet the inclusion criteria will be retrieved in full and their details imported into the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI-SUMARI). The full text of selected citations will be retrieved and assessed independently by two reviewers (SR and EBT) in detail against the inclusion criteria. Full-text studies that do not meet the inclusion criteria will be excluded, and reasons for exclusion will be provided in an appendix in the final systematic review report. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer (FBH).

Assessment of methodological quality
Included studies will be critically appraised by two independent reviewers (SR and EBT) at the study level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute for cohort, cross-sectional surveys and/or case-control study designs (Appendices II and III). The instrument will be amended for our needs. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer (FBH). The results of critical appraisal will be reported in narrative form and in a table.

Data extraction
Data will be extracted from papers included in the review using the standardized data extraction tool for cohort, cross-sectional surveys and/or case-control studies in JBI-SUMARI (Appendices II and III) by two independent reviewers (SR and EBT). We will tailor the extraction form to our needs. The data extracted will include specific details about the exposure of interest including different exposure categories if applicable, populations, study methods and relevant outcomes measures. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer (FBH). Authors of papers will be contacted to request missing or additional data where required.

Data synthesis
Papers will, where possible, be pooled using random effect meta-analysis methods in RevMan 5.3 (Copenhagen, Denmark: The Nordic Cochrane Centre, Cochrane). Effect sizes will be expressed as relative risks (odds ratios or risk ratios) together with their 95% confidence intervals (CIs). If we can assume that the outcome of interest is rare (i.e. <5–10%), then the odds ratio will be very similar to the risk ratio. Effect measures adjusted for confounders will be used in preference to crude effect measures. Where effect estimates and measures of precision (e.g. standard errors, 95% CI) cannot be directly extracted from the included study, we will estimate them from data presented in the paper.

Heterogeneity will be quantified using $I^2$ and $r^2$. Subgroup analyses will be conducted to explore reasons for heterogeneity in the meta-analysis models based on study quality, adjusted versus crude measures of effect, dose of TCS (low versus high), non-melanoma/melanoma and type of patient population (HIV/transplant participants/participants with syndromes versus those without those...
conditions). Where there is insufficient data to allow for meta-analysis, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

We will conduct a sensitivity analysis excluding keratinized epithelium in special sites (e.g. vulvar and penile skin) to determine if there is a difference compared to the overall result. A funnel plot will be generated using RevMan 5.3 to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test and Harbord test) will be performed where appropriate. The GRADE approach for assessing confidence in the quality of evidence will be used for this review, with the results presented in a summary of findings table created using GRADEPro.

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References

1. Daniel BS, Orchard D. Ocular side-effects of topical corticosteroids: what a dermatologist needs to know. Australas J Dermatol 2015;56(3):164–9.
2. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. Health Technol Assess 2001;4(37):191.
3. McHenry PM, Williams HC, Bingham EA. Fortnightly review: management of atopic eczema. BMJ 1995;310:843–7.
4. Van Der Meer JB, Glazenburg EJ, Mulder PG, Eggink HF, Coenraads PJ. The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. The Netherlands Adult Atopic Dermatitis Study Group. Br J Dermatol 1999;140(6):1114–21.
5. Berth-Jones J, Damstra RJ, Golsch S, Livden JK, Van Hoeteghem O, Allegra F, et al. Twice weekly fluticasone propionate added to emollient management treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. BMJ 2003;326(7403):1367.
6. Furue M, Terao H, Rikihisa W, Urabe K, Kinukawa N, Nose Y, et al. Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis. Br J Dermatol 2003;148(1):128–33.
7. Yohn JI, Weston WL. Topical glucocorticosteroids. Curr Probl Dermatol 1990;2:31–63.
8. Bath-Hextall F, Leonard i-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. Int J Cancer 2007;121(9):2105–8.
9. Battistini E, Battistini S, Barachini P. Epidemiology of melanoma and non melanoma skin cancer in the provinces of Pisa and Massa-Carrara from 1997 to 2002. Ital Dermatol Venereol 2005;140(1):33–44.
10. Demers AA, Nugent Z, Mihalciouc I, Wiseman MC, Kliwer EV. Trends of nonmelanoma skin cancer from 1960 through 2000 in a Canadian population. JAAD 2005;53(2):320–8.
11. Hol SA, Malinovszky K, Roberts DL. Changing trends in nonmelanoma skin cancer in South Wales, 1988–98. Br J Dermatol 2000;143(6):1224–9.
12. Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Aust 2006;184(1):6–10.
13. World Health Organization: http://www.who.int/cancer/skincancer/en/index1.html Internet. [Last accessed 1st November 2016]
14. Chen ST, Geller AC, Tsao H. Update on the epidemiology of melanoma. Curr Dermatol Rep 2013;2(1):24–34.
15. Cancer Research UK: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/skin-cancer/mortality Internet. [Last accessed 1st November 2016]
16. Karagas MR, Cushing GL, Greenberg ER, Mott LA, Spencer SK, Nierenberg DW. Non-melanoma skin cancers and glucocorticoid therapy. Br J of Cancer 2001;85(5):683–6.
17. Elmets CA. Oral corticosteroids do not increase the incidence of non-melanoma skin cancers. MD reviewing Baibergenova, A.T. et al. 2012. Oral prednisone use and risk of keratinocyte carcinoma in non-transplant population. The VATTC trial. J Eur Acad Dermatol Venereol 2012;26(9):1109.
18. Hagström L, Ye W, Nyrén O, Emtestam L. Incidence of cancer among patients with atopic dermatitis. Arch Dermatol 2005;141(9):1123–7.
19. Wang H, Diepgen TL. Atopic dermatitis and cancer risk. Br J Dermatol 2006;154(2):205–10.
20. Comeau S, Jensen L, Cockfield SM, Sapijaszko M, Gourishankar S. Non-melanoma skin cancer incidence and risk factors after kidney transplantation: a Canadian experience. Transplantation 2008;86(4):535–41.
21. Ducroux E, Boillot O, Ocampo MA, Decullier E, Roux A, Dumortier J, et al. Skin cancers after liver transplantation: retrospective single-center study on 371 recipients. Transplantation 2014;98(3):335–40.
22. Delgado M, Fernandez R, Paradela M, De La Torre M, Gonzalez D, Garcia JA, et al. Development of neoplasms during lung transplantation follow-up. Transplant Proc 2008;40(9):3094–6.
23. Amital A, Shitrit D, Raviv Y, Bendayan D, Sahar G, Bakal I, et al. Development of malignancy following lung transplantation. Transplantation 2006;81(4):547–51.
24. Muranushi C, Olsen CM, Pandeya N, Green AC. Aspirin and nonsteroidal anti-inflammatory drugs can prevent cutaneous
squamous cell carcinoma: a systematic review and meta-analysis. J Invest Dermatol 2015;135(4): 975–83.

25. Shebl FM, Hsing AW, Park Y, Hollenbeck AR, Chu LW, Meyer TE, et al. Non-steroidal anti-inflammatory drugs use is associated with reduced risk of inflammation-associated cancers: NIH-AARP study. PlusOne 2014;9(12).

26. Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D. Rook’s textbook of dermatology, 4 volume set. 9th ed. Cichester, UK: Wiley-Blackwell; 2016.

27. Williams H, Bigby M, Henxheimer A, Naldi L, Rzany B, Dellavalle R, et al. Evidence-based dermatology. 3rd ed. Oxford, UK: Wiley-Blackwell; 2014.
Appendix I: Search strategy for OVID MEDLINE

Epidemiologic studies/
Exp Case-control studies/
Exp Cohort studies/
Epidemiologic$ stud$.mp.
Case control stud$.mp.
Cohort stud$.mp.
Cohort analy$.mp.
Follow up stud$.mp.
Observational stud$.mp.
Longitudinal.mp.
Retrospective.mp.
Cross sectional stud$.mp.
Cross Sectional Studies/
Exp Observational Study/
Or/1-14
Carcinoma, Basal Cell/
Neoplasms, Basal Cell/
Basal Cell Nevus Syndrome/
Basal cell carcinoma$.mp.
Basal cell cancer$.mp.
Basal cell neoplasm$.mp.
Nodular BCC.mp.
Naevoid BCC.mp.
Gorlin syndrome.mp.
Basal cell Epithelioma$.mp.
Basalioma$.mp.
BCC.mp.
Rodent ulcer$.mp.
Or/16-28
Exp Neoplasms, Squamous cell/
Exp Carcinoma Squamous Cell/
Squamous cell carcinoma$.mp.
Squamous cell cancer$.mp.
Squamous cell neoplasm$.mp.
Bowen's disease.mp.
Planocellular carcinoma$.mp.
SCC.mp.
Or/30-37
Skin neoplasms/
NMSC.mp.
Non melanoma skin cancer$.mp.
Skin cancer$.mp.
Skin tuma$.mp
Skin neoplasm$
Exp Keratinocytes/
Keratinocytes.mp.
Or/38-46
Melanoma/
Melanoma.mp.
Or/48-49
topical corticosteroid$.mp.
steroid$.mp.
corticosteroid$.mp.
exp Glucocorticoids/
alclometasone.mp.
alclomethasone.mp.
amcinonide.mp.
beclometasone.mp.
beclomethasone.mp.
exp Beclomethasone/
betametasone.mp.
betamethasone.mp.
exp Betamethasone/
clobetasol.mp.
exp Clobetasol/
clobetasone.mp.
desonide.mp.
exp Desonide/
desoximetasone.mp.
exp Desoximetasone/
diflorasone.mp.
ediflucortolone.mp.
exp Diflucortolone/
fludroxy cortide.mp.
flumetasone.mp.
exp Flumetasone/
fluocinolone.mp.
exp Fluocinolone Acetonide/
fluocinonide.mp.
exp Fluocinonide/
fluocortolone.mp.
exp Flucortolone/
flurandrenolide.mp.
exp Flurandrenolone/
fluticasone.mp.
halcinonide.mp.
exp Halcinonide/
halobetasol.mp.
halometasone.mp.
hydrocortisone.mp.
exp Hydrocortisone/
methylprednisolone.mp.
exp methylprednisolone/
mometasone.mp.
triamcinolone.mp.
exp Triamcinolone/
Or/ 51-98
15 AND (29 OR 38 OR 47 OR 50) AND 99
Appendix II: Appraisal instruments

**JBI Critical Appraisal Checklist for Comparable Cohort/Case Control**

| Question                                                                 | Yes | No | Unclear | Not Applicable |
|-------------------------------------------------------------------------|-----|----|---------|----------------|
| 1. Is sample representative of patients in the population as a whole?   |     |    |         |                |
| 2. Are the patients at a similar point in the course of their condition/illness? |     |    |         |                |
| 3. Has bias been minimised in relation to selection of cases and of controls? |     |    |         |                |
| 4. Are confounding factors identified and strategies to deal with them stated? |     |    |         |                |
| 5. Are outcomes assessed using objective criteria?                      |     |    |         |                |
| 6. Was follow up carried out over a sufficient time period?             |     |    |         |                |
| 7. Were the outcomes of people who withdrew described and included in the analysis? |     |    |         |                |
| 8. Were outcomes measured in a reliable way?                            |     |    |         |                |
| 9. Was appropriate statistical analysis used?                           |     |    |         |                |

Overall appraisal: Include □ Exclude □ Seek further info. □

Comments (Including reason for exclusion)
Appendix III: Data extraction instrument

**JBI Data Extraction Form for Experimental / Observational Studies**

| Reviewer | Date |
|----------|------|
| Author   | Year |
| Journal  | Record Number |

**Study Method**

- RCT
- Quasi-RCT
- Longitudinal
- Retrospective
- Observational
- Other

**Participants**

- Setting
- Population

**Sample size**

- Group A
- Group B

**Interventions**

- Intervention A
- Intervention B

**Authors Conclusions:**

**Reviewers Conclusions:**
### Study results

#### Dichotomous data

| Outcome | Intervention ( ) number / total number | Intervention ( ) number / total number |
|---------|----------------------------------------|----------------------------------------|
|         |                                        |                                        |
|         |                                        |                                        |
|         |                                        |                                        |

#### Continuous data

| Outcome | Intervention ( ) number / total number | Intervention ( ) number / total number |
|---------|----------------------------------------|----------------------------------------|
|         |                                        |                                        |
|         |                                        |                                        |
|         |                                        |                                        |