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Systemic glucocorticoid use and early-onset basal cell carcinoma

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Introduction

Immunosuppressive medications are common in the management of numerous conditions, such as organ transplantation, allergies, and respiratory disorders [1]. In some patients with conditions, such as organ transplantation, that require long-term, high-dose immunosuppression, immunosuppressives increase risk for squamous cell carcinoma of the skin (SCC) (60–250 fold increase), and to a lesser extent for basal cell carcinoma (BCC) (10 fold increase) [2–10]. An increased risk of non-melanoma skin cancer (NMSC) has also been associated with immunosuppressives among rheumatoid arthritis and inflammatory bowel disease patients [11–13].

With widespread use of low-potency, low-dose immunosuppressives, particularly glucocorticoids, for allergic and inflammatory conditions, there is interest in whether these low-level exposures increase NMSC risk. Glucocorticoids and NMSC have been evaluated in three studies [14–17]. A US case-control study found a two-fold increased risk of SCC with oral glucocorticoids, but only a suggestive non-significant association for BCC [16]. A Danish cohort study using national prescription data found a 16% increase in BCC with injected or oral glucocorticoids, with greater risk with more prescriptions [17]. A case-

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Conflict of Interest
Nothing to declare.

control study in the same Danish population found a 15% increase in BCC with oral glucocorticoids and increased risk with longer duration [15]. There was one positive [17] and one null finding [15] for SCC in the Danish studies. Finally, a US prospective study found no association between oral prednisone and BCC or SCC in adults with prior NMSC [14].

While short-term steroid use is not known to have any lasting impact on immune function, transient immune suppression from systemic steroid use could impact BCC risk, especially in those with high ultraviolet radiation exposure, which may itself induce local immune suppression [18]. To address the paucity of research on systemic glucocorticoids and NMSC, we evaluated this relationship in a case-control study of early-onset BCC.

Materials and Methods

Population

The Yale Study of Skin Health is a case-control study of early-onset BCC in Connecticut (July 2007–December 2010) [19]. BCC cases and randomly selected controls with benign skin conditions were identified from Yale Dermatopathology. Eligible participants were ≤40 years at skin biopsy, Connecticut residents, and proficient in English. 389 BCC cases (participation rate=72.8%) and 458 controls (participation rate=60.7%) frequency matched on age at biopsy, gender, and biopsy site were enrolled and completed in-person interviews. The most common control conditions were cyst (16.4%), seborrheic keratosis (16.2%), and wart (11.4%). Yale University's Institutional Review Board approved the study and participants provided written informed consent.

Glucocorticoids

We assessed immunosuppressive medication use up to one year before the in-person interview, showing participants a list of common oral or injected medications (e.g. cortisone, dexamethasone, prednisolone, prednisone) to aid recall. Interviewers gathered medication name, medical indication, age started and stopped, and number of days per year on the medication. Dosage was not queried. The study physician (AEB) reviewed the concordance between medication and indication while blinded to case-status as a quality control check.

Statistical Analysis

Our non-Hispanic white analytic sample included 364 cases and 379 controls. Three BCC cases with Gorlin syndrome [20] were excluded, as were three cases with missing immunosuppressive medication data, one case reporting solid organ transplantation, three cases with valid medication, but an invalid medical indication, and six cases and 11 controls reporting any non-glucocorticoid immunosuppressive use.

Odds ratios (ORs) and 95% confidence intervals (CIs) were computed using multivariate unconditional logistic regression (SAS Version 9.2, Cary, NC). The multivariate models included variables that were significantly associated with BCC or altered risk estimates by ≥ 10%.

Results

The population has been described in detail elsewhere [21]. 133 (36.5%) cases and 153 (40.4%) controls used glucocorticoids. The most common medications were prednisone (53.8%) and cortisone (22.0%). The most common indications were poison ivy/oak/sumac (28.5%), asthma/other respiratory (20.9%), and other dermatological conditions (e.g. hives, rash) (19.1%). Indication did not vary by case-status.

There was no association between ever use of glucocorticoids and early-onset BCC (OR=0.81, 95% CI=0.58–1.14) (Table 1). Similarly, we did not observe an association by duration of use (≥30 days vs. no use OR=0.70, 95% CI=0.38–1.30).

Participants could not recall the names of 22.5% of the immunosuppressives, but the medical indications they reported were consistent with glucocorticoids. Results remained unchanged in sensitivity analyses where the unknown medications were removed from the analysis or were assumed to have been taken either <30 or ≥30 days.

Discussion

We saw no evidence of an association between systemic glucocorticoids and early-onset BCC.

Existing data on glucocorticoids and BCC are limited to three older-age populations [14–17]; one observed a positive association [15, 17] and two had null findings [14, 16]. Our null findings could be explained by a long latency period between glucocorticoid exposure and BCC; such an association may not have manifested in our younger population. Also, if cumulative dose is relevant, young populations may not have sufficient exposure to impact risk.

Our study had several strengths, including medical indication and duration data. Whereas the Danish studies [15, 17] did not have skin cancer risk factor data, we had data on host characteristics and ultraviolet radiation exposures. Our study also had some limitations. With self-reported measures there may have been errors in glucocorticoid reporting. Recall was unlikely to differ by case-status, but there may have been random error in both groups. We also did not assess inhaled glucocorticoids, though inhaled medications were not associated with NMSC in another study [16]. Further, while medical indication for glucocorticoids did not vary by case status, we lack data on why participants sought dermatologic care and this may have differed by case-status.

We lacked dosage information, but we estimated potency of different glucocorticoids by standardizing all medications to the anti-inflammatory equivalent of hydrocortisone [22, 23]. We then assigned a specific daily dose of hydrocortisone for each medical indication. In an exploratory analysis, we estimated a total intensity measure by multiplying each indication and medication specific dose by the corresponding duration of use and then summed across all medications. There was no trend toward greater BCC risk with greater intensity (dose x duration); risk estimates mirrored those for duration only (data not shown).

In summary, we found no evidence that systemic glucocorticoids increase the risk of BCC in young people, some of whom had substantial ultraviolet radiation exposure from indoor/outdoor tanning. This is consistent with findings for oral prednisone in higher risk US adults [14]. Two other studies in older populations found stronger associations with glucocorticoids and SCC than BCC; consistent with NMSC patterns observed in immunosuppressed patients. The possibility remains that long-term low-dose glucocorticoid use contributes to BCC risk in older populations, but our study is reassuring, with no evidence of an adverse effect in young, healthy people.

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Abbreviations

BCC	basal cell carcinoma
CI	confidence interval
NMSC	non-melanoma skin cancer
OR	odds ratio
SCC	squamous cell carcinoma

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Table 1

Odds ratios and 95% confidence intervals for association between systemic glucocorticoid use and early-onset BCC in the Yale Study of Skin Health

Characteristic	Cases/Controls	Multivariate OR[1] (95% CI)	P-Trend[2]
Use of Glucocorticoids			-
No	230/222	1.00	
Yes	132/150	0.81 (0.58–1.14)	
Duration of Glucocorticoid Use			0.153
No use (0 days)	230/222	1.00	
1–29 days	99/105	0.81 (0.56–1.18)	
≥ 30 days	23/37	0.70 (0.38–1.30)	

Abbreviations: CI, Confidence Interval; MC1R, melanocortin 1 receptor; OR, odds ratio.

[1] Adjusted for age at diagnosis (continuous, years), gender, body site of skin biopsy (head, extremity, trunk), hair color (black/dark brown, light brown, blonde/fair, red), skin color (olive, fair, very fair), *MC1R* non-synonymous variants (0, 1, ≥2), family history of skin cancer (yes, no), ever indoor tanning (yes, no), and sun exposure in warm months (continuous, hours).

[2] Based on an ordinal categorical variable.