Incidence of skin cancers in patients with eczema treated with ultraviolet phototherapy

To the Editor: Ultraviolet B (UVB) phototherapy is commonly used in cases of eczema, but its carcinogenic risk has not been specifically assessed in this setting. Population studies suggest that patients with atopic eczema have higher incidences of skin cancer and lymphoma, with other studies reporting no association.[1,2] Not only is atopic eczema associated with underlying immune dysregulation, but certain treatments are potentially carcinogenic. Studies have assessed the risk of phototherapy carcinogenesis for psoriasis and vitiligo but not eczema.[3,4] We sought to investigate whether patients with eczema treated with ultraviolet phototherapy have a higher risk of skin cancer by performing a retrospective cohort study at a teaching hospital phototherapy clinic (1996-2018). Skin cancer records were validated via centralized pathology database reports.

Nine hundred twenty-five patients with eczema receiving broadband UVB, narrowband UVB, or concurrent UVA plus broadband UVB were assessed, with a median follow-up of 5.1 years (0.6-22.7 years) (end of follow-up June 2019) (Fig 1). Patients who received psoralen plus UVA (PUVA) were excluded. Patient demographics are shown in Supplemental Table S1 (available via Mendeley at http://doi.org/10.17632/tb35f835dz.1).

Overall, 34 skin cancers (4 melanomas, 10 squamous cell carcinomas, and 20 basal cell carcinomas) occurred in 14 patients post phototherapy (Supplemental Table S2, available via Mendeley at http://doi.org/10.17632/tb35f835dz.1).

The patient-based age-standardized incidence rate (ASIR) (the number of patients with a first occurrence of skin cancer after phototherapy) and the case-based ASIR (the total number of new skin cancers post phototherapy) were 137 (95% CI 59-216) per 100,000 person-years and 256 (95% CI 157-354) per 100,000 person-years, respectively.

Case-based ASIRs were compared with the 2003 British Columbia provincial population, which reported ASIRs by gender (Table I).[5] The reported provincial keratinocyte cancer ASIR is likely to be lower than the actual population case incidence since not all instances of multiple keratinocyte cancers are included in this cancer registry. Nevertheless, no significant difference was found between melanoma, squamous cell carcinoma ($P > .05$), or basal cell carcinoma ($P > .05$) case-based ASIRs in patients with eczema undergoing ultraviolet phototherapy and the provincial population (male). Due to limited numbers of melanomas and female skin cancer cases, Z-test analysis was not performed.

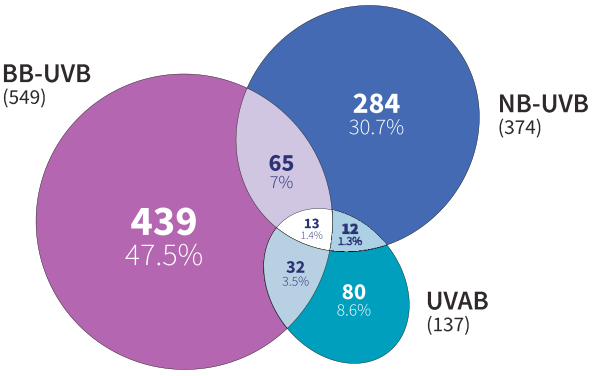

Fig 1. Distribution of modalities used by 925 patients with eczema receiving one or more different forms of ultraviolet phototherapy. The number after each modality label indicates the total number of patients who received that form of phototherapy. The numbers within the overlapping Euler diagram ellipses indicate the numbers (and percentages) of patients receiving single versus multiple sequential phototherapy modalities. *BB-UVB*, Broadband ultraviolet B; *NB-UVB*, narrowband ultraviolet B; *UVAB*, concurrent ultraviolet A plus BB-UVB.

The anatomical distribution of cancers was mostly on the head and neck, consistent with sun exposure as a primary causal factor. Skin cancer incidence increased with age; the mean age of affected patients was 71 years (range 37-89).

Patients undergoing phototherapy who had a history of taking immunosuppressive medications had an increased risk of skin cancer ($P < .05$; odds ratio 7.2) compared to those not receiving immunosuppressants (Supplemental Table S3, available via Mendeley at http://doi.org/10.17632/tb35f835dz.1).

We also evaluated skin cancer risk based on the total amount of phototherapy received. No significant difference in case-based ASIRs was seen in patients treated with ≤25 sessions (1 treatment course) versus >25 or >100 sessions (Supplemental Table S4, available via Mendeley at http://doi.org/10.17632/tb35f835dz.1). This should be interpreted cautiously, as although the range of UVB treatments received was wide (1-1270; median 29), only 125 patients (13%) received >100 sessions.

Although the follow-up duration, number of patients and lack of pediatric cases are potential limitations, the advantages of our study include the validation of skin cancer diagnoses via pathology

Table I. Age-standardized incidence rates (95% CI) of skin cancer in patients with eczema receiving ultraviolet phototherapy compared to the general population

	Patient-based ASIR* event/100,000 p-y (95% CI)	Case-based ASIR* (male) event/100,000 p-y (95% CI)	British Columbia male population ASIR*† event/100,000 p-y
Follow-up years	4917	4939	
All skin cancers	137 (59-216)	360 (213-507)	
Melanoma	11 (0-32)	40 (0-82)	16‡
KC	126 (51-202)	320 (178-461)	
BCC	79 (19-139)	209 (104-315)	189§
SCC	47 (1-93)	110 (27-193)	53§

ASIR, Age-standardized incidence rate; *BCC*, basal cell carcinoma; *KC*, keratinocyte carcinoma (includes BCCs and SCCs); *SCC*, squamous cell carcinoma; *p-y*, person-years.

*ASIR age standardized to the 1991 Canadian general population as reported on "Statistics Canada."[5] Statistical analysis: Z-test used to test differences between incidence rates (R Foundation for Statistical Computing, version 3.6.1, 2019). Male case-based ASIR compared to the British Columbia male population ASIR. Due to limited numbers of female skin cancer cases and melanomas, Z-test analysis was not performed.

†Comparison to 2003 British Columbia male population age-standardized incidence rate which includes:

‡All cases of melanomas, including multiple melanomas in an individual patient.

§Not all multiple BCC or SCC occurrences included in cancer registry (second primary BCCs and SCCs coded as unspecified site tumors included).[5]

reports and the evaluation of multiple skin cancers versus first-registered cancers only.

Overall, other than for patients with a history of taking immunosuppressive therapy, there was no increased risk of melanoma, squamous cell carcinoma, or basal cell carcinoma in patients receiving ultraviolet phototherapy, including narrowband UVB, broadband UVB, and concurrent UVA plus broadband UVB, supporting this as a non-carcinogenic treatment for patients with atopic eczema.

Tashmeeta Ahad, BM BCh, MA(Cantab), MRCP,[a,b] *Elle Yueqiao Wang, Msc,*[a,b] *Yi A. Liu, MD,*[c] *Tim K. Lee, PhD,*[a,b,d] *Harvey Lui, MD, FRCPC,*[a,b] *Richard I. Crawford, MD,*[c] *and Sunil Kalia, MD, MHSc, FRCPC*[a,b,d,e,f]

From the Department of Dermatology and Skin Science, University of British Columbia, Vancouver, Canada[a]*; the Photomedicine Institute, Vancouver Coastal Health Research Institute, Canada*[b]*; Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada*[c]*; the Department of Cancer Control Research, BC Cancer, Vancouver, Canada*[d]*; BC Children's Hospital Research Institute, Vancouver, Canada*[e]*; and the Clinical Centre for Epidemiology and Evaluation, Vancouver Coastal Health Research Institute, Canada.*[f]

Drs Ahad and Wang contributed equally as cofirst authors.

Funding sources: Supported by research grants from the Eczema Society of Canada (F16-05485) and Canadian Dermatology Foundation. Dr Ahad was funded by The Geoffrey Dowling Fellowship from the British Association of Dermatologists and by funds donated by Mr Lindsay Hall to the University of British Columbia. Dr Kalia was funded by the Photomedicine Institute, Vancouver General Hospital, and University of British Columbia Hospital Foundation and Michael Smith Foundation for Health Research (18609). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

IRB approval status: This study was reviewed and approved by the University of British Columbia Clinical Research Ethics Board (CREB #H17-03410).

Key words: atopic dermatitis; atopic eczema; basal cell carcinoma; broadband UVB; eczema; incidence; melanoma; narrowband UVB; phototherapy; skin cancer; squamous cell carcinoma; ultraviolet B; ultraviolet light; UVA; UVB.

Reprints not available from the authors.

Correspondence to: Sunil Kalia, MD, MHSc, FRCPC, University of British Columbia, Department of Dermatology and Skin Science, 835 West 10th Avenue, Vancouver, British Columbia, Canada, V5Z 4E8

E-mail: sunil.kalia@vch.ca

Conflicts of interest

None disclosed.

REFERENCES

1. Arana A, Wentworth CE, Fernández-Vidaurre C, Schlienger RG, Conde E, Arellano FM. Incidence of cancer in the general population and in patients with or without atopic dermatitis in the U.K. *Br J Dermatol*. 2010;163(5):1036-1043.
2. Ming ME, Levy R, Hoffstad O, et al. The lack of a relationship between atopic dermatitis and nonmelanoma skin cancers. *J Am Acad Dermatol*. 2004;50(3):357-362.
3. Hearn RM, Kerr AC, Rahim KF, Ferguson J, Dawe RS. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. *Br J Dermatol*. 2008;159(4):931-935.
4. Bae JM, Ju HJ, Lee RW, et al. Evaluation for skin cancer and precancer in patients with vitiligo treated with long-term narrow-band UV-B phototherapy. *JAMA Dermatol*. 2020;156(5):529-537.
5. Mclean DI, Phillips N, Zhou Y, Gallagher R, Lee TK. 40-year trends in skin cancer in British Columbia, Canada, 1973 to 2003. *J Cutan Med Surg*. 2012;16(2):83-91.

https://doi.org/10.1016/j.jaad.2021.11.048

Placebo group regrowth rate in alopecia areata clinical trials: A systematic review and meta-analysis

To the Editor: Alopecia areata (AA) is an autoimmune disorder that causes hair loss and has an unpredictable course.[1] The identification of Janus kinase inhibitors for use in patients with AA has led to multiple studies evaluating novel therapeutics.[2] Although placebo-controlled trials remain the gold standard, recruiting and maintaining patients to receive placebo treatment can be challenging because patients may be subjected to months of therapy, with no potential benefit. Herein, we assessed placebo group regrowth rates (PGRRs) across AA clinical trials.

Studies were identified by searching Medline or PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (Supplementary Material 1, available via Mendeley at https://data.mendeley.com/datasets/kvvzkb26jr/1). All published AA clinical trials assessing PGRR were investigated. Publications not in English were excluded. Titles and abstracts were screened independently twice (Authors Desai and Li) using Covidence (www.covidence.org), with a third reviewer (Dr Mostaghimi) resolving disagreements.

Included studies were classified into 2 groups: (1) patchy alopecia, including studies only treating affected patch(es) or if patients had <50% scalp involvement and (2) severe alopecia, including studies with patients with >50% scalp involvement (Supplemental Material 2, available via Mendeley at https://data.mendeley.com/datasets/kvvzkb26jr/1). Data on PGRR, defined as hair regrowth among patients not receiving active treatment, were extracted by 1 investigator (Author Desai). The study protocol was registered with the Prospective Register of Systematic Reviews (PROSPERO) (CRD42020166272).

The outcome of PGRR was the proportion achieving ≥50% regrowth, which was analyzed separately for patchy and severe AA. A random-effects meta-analysis pooled the estimates of the proportions achieving ≥50% regrowth. The

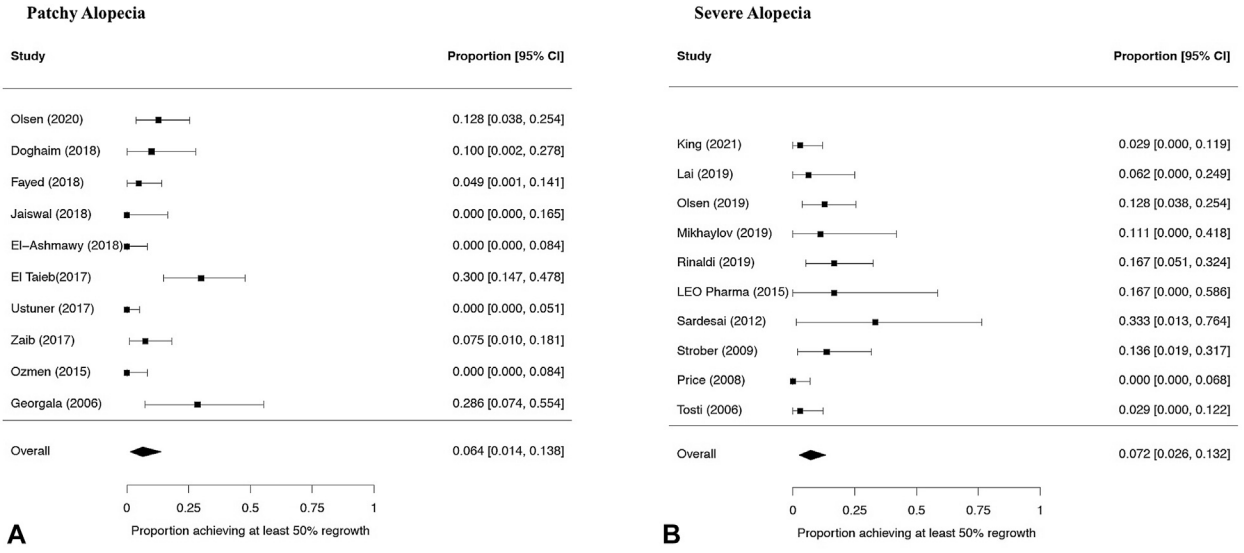

Fig 1. Forest plots of placebo group regrowth rates in alopecia areata clinical trials. **A,** Pooled placebo group regrowth rate among 10 clinical trials for patchy alopecia. **B,** Pooled placebo group regrowth rate among 10 clinical trials for severe alopecia.