nail unit, including the hyponychium, in pediatric patients with longitudinal melanonychia. We propose that hyponychial LBP is a distinctive dermoscopic feature observed in pediatric longitudinal melanonychia and that its presence supports the clinical impression of NMN in pediatric patients.

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Conflicts of interest

None disclosed.

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Anti–tumor necrosis factor therapy is associated with increased in situ squamous cell carcinoma of the skin: A population-based case-control study

To the Editor: Tumor necrosis factor inhibitors (TNFis) have been associated with an increased risk of keratinocyte carcinoma in patients with rheumatoid arthritis and psoriasis, but population-wide data are lacking.[1-3] A population-based case-control study was performed to analyze the association between TNFis and keratinocyte carcinoma using the Icelandic Cancer Registry and the Icelandic Prescription Medicine Register.[4,5] All patients with an initial, histologically confirmed diagnosis of invasive squamous cell carcinoma (SCC), SCC in situ (SCCis), or basal cell carcinoma (BCC) were included as cases and were identified using an *International Classification of Diseases, 10th revision* code between 2003 and 2017. Patients taking cyclosporine, azathioprine, or mycophenolate mofetil were excluded. Risk-set sampling was used to pair each case with 10 age- and sex-matched control subjects. Patients were considered exposed to TNFi if they filled ≥1 prescription for adalimumab, etanercept, infliximab, or golimumab before their first diagnosis of keratinocyte carcinoma. Multivariable conditional logistic regression was performed and adjusted for age, sex, and the use of photosensitizing medications (tetracyclines or oral and topical retinoids) and hydrochlorothiazide. Adjusted odds ratio (aORs) and 95% confidence intervals (CIs) were estimated.

Four thousand seven hundred patients with BCC, 1013 with invasive SCC, and 1167 with SCCis and 47,293, 10,367, and 11,961 control subjects, respectively, were identified (Table I). TNFi exposure was associated with an increased risk of SCCis (aOR 3.13 [95% CI 1.15-8.55]; Table II) but not invasive SCC. Overall TNFi exposure was not associated with risk of BCC (aOR 1.68 [95% CI 0.91-3.11]).

This population-based study shows a significantly increased risk of SCCis, but not invasive SCC, among TNFi users compared with the general Icelandic population. While other studies found an association between TNFi and SCC,[2,3] they did not separate invasive SCC and SCCis in their analyses. It is possible that our study was not powered to detect differences in invasive SCC and BCC risk. Iceland has a low level of background ultraviolet light exposure in a population that is almost exclusively white. The SCCis risk increase with TNFi exposure could be even greater in regions with higher exposure to ultraviolet light. This study differs from the Swedish population-based study of TNFi and keratinocyte carcinoma in that it includes all patients taking TNFis, whereas the Swedish study only studied patients with rheumatoid arthritis.[2] Previous studies have not shown an increased risk of BCC with TNFi use.[2,3]

Study limitations include the inability to adjust for sun exposure, patient comorbidities, and indication for TNFi use. Similarly, we were unable to adjust for exposure to phototherapy, which may have been

Table I. Summary of patients with SCC, SCCis, and BCC and age- and sex-matched control subjects

	Invasive SCC		SCCis		BCC	
Characteristic	Case, n = 1013	Control, n = 10,367	Case, n = 1167	Control, n = 11,961	Case, n = 4700	Control, n = 47,293
Age, median (IQR)	79 (71-85)	79 (70-85)	77 (67-84)	77 (67-84)	69 (56-79)	69 (56-79)
Male sex, n (%)	521 (51.43)	5309 (51.21)	425 (36.42)	4368 (36.52)	1988 (42.30)	20,023 (42.34)
Use of PM, n (%)	403 (39.78)	3597 (34.70)	483 (41.39)	4430 (37.04)	1735 (36.91)	15,810 (33.43)
Use of HCTZ, n (%)	90 (8.88)	894 (8.62)	116 (9.94)	979 (8.18)	346 (7.36)	3065 (6.48)
Use of TNFi, n (%)	3 (0.30)	16 (0.15)	5 (0.43)	19 (0.16)	12 (0.26)	70 (0.15)

BCC, Basal cell carcinoma; *HCTZ*, hydrochlorothiazide; *IQR*, interquartile range; *PM*, photosensitizing medications, including tetracyclines and retinoids; *SCC*, squamous cell carcinoma; *SCCis*, SCC in situ; *TNFi*, tumor necrosis factor alpha inhibitor.

Table II. Association between TNFi exposure and incidence of BCC and SCC with subgroup analysis

	Cases exposed/unexposed	Control subjects exposed/unexposed	Adjusted OR (95% CI)*
Invasive SCC	3/1010	16/10,351	1.80 (0.51-6.34)
Male	1/520	7/5302	1.37 (0.16-11.66)
Female	2/490	9/5049	2.10 (0.44-10.09)
<50 y	1/34	0/380	N/A
≥50 y	2/976	16/9971	1.19 (0.27-5.31)
SCCis	5/1162	19/11,942	3.13 (1.15-8.55)
Male	1/424	3/4365	5.02 (0.45-55.69)
Female	4/738	16/7577	2.84 (0.93-8.63)
<50 y	0/64	2/673	N/A
≥50 y	5/1098	17/11,269	3.37 (1.22-9.28)
BCC	12/4688	70/47,223	1.68 (0.91-3.11)
Male	4/1984	21/20,002	1.82 (0.62-5.36)
Female	8/2704	49/27,221	1.62 (0.76-3.42)
<50 y	1/746	9/7509	1.00 (0.12-8.13)
≥50 y	11/3942	61/39,714	1.78 (0.93-3.38)

BCC, Basal cell carcinoma; *CI*, confidence interval; *N/A*, not available; *OR*, odds ratio; *SCC*, squamous cell carcinoma; *SCCis*, SCC in situ; *TNFi*, tumor necrosis factor alpha inhibitor.
*Odds ratio adjusted for use of oral and topical retinoids, tetracyclines, and hydrochlorothiazide.

disproportionately higher in individuals exposed to TNFi. In addition, only patients taking adalimumab, etanercept, infliximab, and golimumab were evaluated because these were the only TNFis prescribed significantly in Iceland during this timeframe.

In conclusion, this population-based study suggests that individuals receiving TNFis are at an elevated risk of developing SCCis in a low ultraviolet light environment. Sun protective behaviors alone might not eliminate this risk. TNFi-induced immunosuppression might play a larger role in the pathogenesis of SCCis compared with BCC.

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The chronic use of multiple photosensitizing drugs is associated with Breslow thickness in female melanoma patients: A bicentric retrospective study

To the Editor: Pharmacopoeia encompasses a wide spectrum of molecules known to have a photosensitizing effect.[1] Both experimental and epidemiologic studies suggest that photosensitizing drugs, especially antihypertensive agents, may influence the incidence of skin cancer.[2,3] The objective of our study was to investigate a possible association between the intake of photosensitizing drugs and Breslow thickness (BT) among melanoma patients. The study was retrospectively performed at inpatient wards of melanoma units from 2 different hospitals: IDI-IRCCS in Rome and University Hospital Sant'Orsola-Malpighi in Bologna, Italy. A total of 554 patients with cutaneous melanoma met the inclusion criteria and were enrolled in the study. Data on socio-demographic variables, histologic variables, skin phototype, and sun exposure and clinical variables, including the presence of chronic diseases, the regular use of drugs, and the body mass index (BMI), were collected. To investigate a possible association between photosensitizing drug use and BT, the Cumulative Logit Model was used. Sex, age, center, ulceration, mitotic rate, anatomic site of the lesion, BMI, the presence of chronic diseases, skin phototype, and sun exposure were considered potential confounders. Statistically significant variables were included in the final multivariate model. The likelihood-ratio test was used to test for interactions. Because the non−drug users may differ from the users on uncontrolled confounders, we also included in the model an indication of drug use. To test if the effect of photosensitizing drug exposure would increase systematically with the level of BT (dose-response), we included the intensity of photosensitizing drugs use as an ordinal variable in the logit model and tested for any trends (Wald test). The statistical software used was package STATA, release 15 (StataCorp LLC, College Station, TX).

Table I shows the demographic, clinical, and histologic characteristics of the subjects as well as drug use and association with BT together with a univariate analysis.

In the multivariate model, after adjusting for age, center, BMI, skin phototype, and sun exposure, women taking 2 or more photosensitizing drugs had 3 times an increased risk of a thicker melanoma compared with non−drug users (odds ratio [OR], 3.77; 95% confidence interval [CI], 1.36-10.4, *P*-trend = .003). This result seemed to be caused by the calcium channel blockers (OR, 3.32; 95% CI, 1.00-11.0; $P = .049$). However, no association was found among men (OR, 1.0; 95% CI, 0.40-2.55) (Table II). This finding may be explained by the gender differences in the cancer biology, genetic background, pharmacokinetics, and immune response or by differences in the behavior toward sun exposure and healthcare.[4] The mean BT in men was 1.3 mm (standard deviation, 1.6) and 1.0 mm (standard deviation, 1.5) in women ($P = .071$).

The limitations of this study include the low number of participants, its retrospective nature, and the possible recall bias.

Further studies with a larger sample size are necessary. Because of population aging and an increased life expectancy, there is a high prevalence of the so-called polypharmacy to treat chronic diseases. The effects of the drugs on photosensitization can be subclinical and go unnoticed. Long-term surveillance may be indicated together with photoprotection as an effective form of cancer prevention in patients receiving multiple drugs.[5]

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