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Brief Communication

BRIEF COMMUNICATION

Association of Indoor Tanning Exposure With Age at Melanoma Diagnosis and *BRAF* V600E Mutations

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Abstract

There is limited information on how indoor tanning promotes melanoma development. We investigated indoor tanning use in patients with melanomas in sun-exposed skin and studied the clinicopathological and molecular characteristics in relation to indoor tanning exposure. Patients from a multidisciplinary clinic for cutaneous cancers completed standardized questionnaires on risk factors for melanoma as a component of medical history at their initial consultations. For this study, we included patients from December 2013 to May 2015. The 114 patients who reported indoor tanning exposure were younger at diagnosis than the 222 patients who did not (51.5 vs 64.0 years, two-sided $P < .001$). *BRAF* V600E genotype was more prevalent in ever-users than in nonusers (42.9% vs 28.3%, two-sided $P = .04$) and higher in ever-users who initiated indoor tanning prior to age 25 years compared with age 25 years or older (62.2% vs 31.1%, two-sided $P = .003$). There were more melanomas in intermittently sun-exposed skin in ever-users than nonusers (65.7% vs 51.9%, respectively, two-sided $P = .02$). Our data suggest indoor tanning may promote melanomas that arise in skin with low-chronic sun-induced damage through *BRAF* V600E-mediated melanomagenesis.

There are distinct molecular pathways leading to melanomas, and ultraviolet radiation is the principal cause of melanomas in sun-exposed skin, but not melanomas of sun-shielded sites (1–4). Indoor tanning is linked to increased risk of melanoma, particularly with first use at a younger age (5–8). There is limited information on how indoor tanning promotes melanoma development. We investigated indoor tanning exposure in melanoma patients and studied the clinicopathological and molecular characteristics in relation to indoor tanning exposure.

We enrolled patients with a histological diagnosis of melanoma from December 2013 to May 2015 from a multidisciplinary clinic for cutaneous cancers. Patients completed standardized questionnaires on risk factors for melanoma as a component of medical history at their initial consultations. We assigned skin type by Fitzpatrick classification (9) and measured sun exposure by sun-seeking behavior, sunburns during childhood and adulthood, and tendency to have tanned skin. We assessed indoor tanning exposure by age at initiation, session length and frequency, and duration by groupings of age younger than 18 years, 18–34 years, and older than 34 years. We extracted clinical data from medical records and the Alberta Cancer Registry. The Health Research Ethics Board of Alberta, Cancer Committee approved the study with patient informed consent waived (CC-15–0008).

The analysis included cutaneous melanomas, excluding ocular, mucosal, and acral-lentiginous melanomas. Fisher exact tests were used to analyze categorical data. Wilcoxon rank-sum tests were performed to study continuous variables. Multivariable linear regression via ordinary least-squares approach was used to jointly evaluate the effect of indoor tanning and covariates. The effect was validated by an additional linear regression via least absolute deviations. Statistical analyses were conducted in R v3.3.0 (10). *P* values were two-sided at a 5% level of statistical significance.

Of the 339 patients (median age = 62.2 years [range 20.6–90.0 years] at enrollment; 44.2% women), 114 (33.6%) reported having

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Table 1. Age at melanoma diagnosis in ever-users and nonusers in total and in subgroups by sex, skin type*, and family history

Characteristic	Ever-users†		Nonusers†		P
	No.	Median (range) age, y	No.	Median (range) age, y	
Total	114	51.5 (15.0–84.0)	222	64.0 (21.0–89.0)	<.001‡
Women	64	50.5 (23.0–84.0)	83	61.0 (21.0–87.0)	<.001
Men	50	53.0 (15.0–81.0)	139	65.0 (21.0–89.0)	<.001
Skin type					
Type 1	9	48.0 (15.0–63.0)	19	59.0 (40.0–83.0)	.04
Type 2	100	52.5 (23.0–84.0)	194	65.0 (21.0–89.0)	<.001
Type 3	3	53.0 (50.0–53.0)	8	59.0 (28.0–84.0)	.54
Family history of melanoma					
No	85	51.0 (15.0–84.0)	167	65.0 (21.0–89.0)	<.001
Yes	23	53.0 (23.0–66.0)	37	54.0 (26.0–83.0)	.08

*Skin type was determined by the color of skin in the axillary vault and skin reaction to ambient and intense sun exposure according to the Fitzpatrick classification of skin type I–VI (I being fairest, burns easily, and never tans). Only one patient had skin type IV; therefore, analysis was not performed for skin type IV.
†Three individuals were excluded from the total of 339 patients due to missing indoor tanning data. Numbers do not total 114 for ever-users and 222 for nonusers cohort in skin type due to skin type IV not being included and in family history of melanoma due to missing data.
‡Multivariable linear regression via ordinary least-squares approach was used to jointly evaluate the effect of indoor tanning and covariates including sex, skin type, hair color, eye color, sun exposure, and family history for the total group. The estimated effect of indoor tanning on age at diagnosis was −10.1 years (95% confidence interval −6.6 to −13.6 years, $P < .001$). The analysis was validated by an additional linear regression via least absolute deviations with similar conclusion.

used indoor tanning at least once in their lifetime (ever-users) and 222 (65.5%) reported never having used indoor tanning (nonusers). At enrollment, ever-users were younger than nonusers (median age 55.0 vs 67.3 years, $P < .001$) and more likely to be female (56.1% [64 of 114] vs 37.4% [83 of 222], $P = .001$). Patients were fair-skinned (96% skin types I or II in both cohorts) with no statistically significant differences in hair color, eye color, number of moles, or family history between cohorts. More ever-users reported a history of sunburns during childhood or adulthood and a higher tendency to have tanned skin (Supplementary Table 1, available online).

Women reported shorter session lengths; otherwise the usage patterns between women and men were similar. Median age at indoor tanning initiation was 30 years (range = 13–70 years), with a median session length of 10 minutes (range = 3–30 minutes), for a median of 5 years (range = 0–38 years), and a median total dose of 15 sessions (range = 1–10 220) (Supplementary Table 2, available online).

Ever-users were statistically significantly younger at diagnosis than nonusers (median 51.5 vs 64.0 years; mean 50.3 vs 62.0 years, $P < .001$ as shown in Table 1). After adjusting for sex, skin type, hair color, eye color, sun exposure, and family history, the estimated effect of indoor tanning on age at diagnosis was 10.1 years earlier (95% confidence interval −6.6 to −13.6 years, $P < .001$). The association between indoor tanning and younger age at diagnosis was statistically significant within women (50.5 vs 61.0 years, $P < .001$), men (53.0 vs 65.0 years, $P < .001$), skin type I (48.0 vs 59.0 years, $P = .04$), skin type II (52.5 vs 65.0 years, $P < .001$), or negative family history (51.0 vs 65.0 years, $P < .001$). A similar trend was seen in patients with positive family history but was not statistically significant, likely due to the small sample size (Table 1).

Among baseline clinicopathological characteristics, we found more melanomas in intermittently sun-exposed skin (trunk and proximal extremities) in ever-users than nonusers (65.7% vs 51.9%, $P = .02$) (Table 2). We did not find statistically significant differences in primary tumor thickness, ulceration status, mitotic rate, tumor infiltrating lymphocytes, regression, or staging between cohorts.

BRAF mutation status in exon 15 was assessed by real-time polymerase chain reaction using the Qiagen *BRAF* RGQ PCR Kit as standard care. *BRAF* mutation status was available from 98 of 115 (86.0%) melanomas in ever-users and 191 of 227 (86.0%) in nonusers. Overall, 105 of 289 (36.3%) melanomas were *BRAF*-mutant, of which 96 (91.4%) were V600E, 7 were V600K, and 2 were V600R. *BRAF* V600E was more prevalent in ever-users than nonusers (42.9% vs 28.3%, $P = .04$) (Table 2) and higher in those initiated prior to age 25 years compared with those 25 years or older (62.2% vs 31.1%, $P = .003$, data not shown). *BRAF* V600E mutations were more frequent in melanomas arising on the trunk and proximal extremities than on the head and neck and distal extremities (43.8% [64 of 146] vs 20.8% [25 of 120], $P < .001$). In each anatomic group, *BRAF* V600E mutations were more frequent in ever-users than nonusers, but these differences did not reach statistical significance (50.0% [29 of 58] vs 39.8% [35 of 88] in trunk and proximal extremity melanomas [$P = .24$] and 32.4% [11 of 34] vs 16.3% [14 of 86] in head and neck and distal extremity melanomas [$P = .08$]).

In summary, we found that indoor tanning exposure is associated with melanomas in intermittently sun-exposed skin, younger age at diagnosis, and *BRAF* V600E mutations. Previous work has linked indoor tanning to early-onset melanomas (12–14) and truncal location (13,15,16). Data collectively suggest that indoor tanning may promote low-chronic sun-induced damage (CSD) melanomas through the *BRAF* V600E-mediated pathway. Low-CSD melanomas arise in intermittently sun-exposed skin in younger adults (3,4,17). They frequently arise from precursor nevi, which already carry the *BRAF* V600E mutation but acquire additional mutations through ultraviolet exposure (18). Nevi as potential melanoma precursors have a limited life span, because they start to involute in the fourth decade of life, possibly explaining the marked decrease of low-CSD melanomas in older adults (4,18,19). By contrast, CSD melanomas affect older individuals, arise primarily on the head and neck and distal extremities, and are not associated with nevi.

Our results need to be interpreted with caution given the small sample size from a single center. Other important limitations include potential imbalances in host constitutional factors and sun exposure between cohorts, birth-cohort effect, and potential survivor bias. Indoor tanning use is associated with poor sun-protection behaviors (20). However, meta-analyses conclude that any indoor tanning exposure increases risk of

Table 2. Clinical and tumor characteristics in ever-users and nonusers*

Characteristic	Cohorts†, No. (%) Ever-users (n = 114)	Nonusers (n = 222)	P‡
BRAF status§			
Available	98 (86.0)	191 (86.0)	.04
V600E	42 (42.9)	54 (28.3)	
Non-V600E	2 (2)	7 (3.7)	
Wild type	54 (55.1)	130 (68.1)	
Not available	16 (14.0)	31 (14.0)	
Location of primary tumor			.02
Known primary	108 (94.7)	206 (92.8)	
Trunk and proximal extremity	71 (65.7)	107 (51.9)	
Head/neck and distal extremity	37 (34.3)	98 (47.6)	
Not available	0 (0)	1 (0.5)	
Unknown primary	6 (5.3)	16 (7.2)	
Not available	0	0	
Tumor characteristics‖	108	206	
Tumor stage			.36
T0	1 (0.9)	1 (0.5)	
T_1	26 (24.1)	40 (19.4)	
T_2	41 (38.0)	60 (29.1)	
T_3	19 (17.6)	49 (23.8)	
T_4	20 (18.5)	52 (25.2)	
Not available	1 (0.9)	4 (1.9)	
Ulceration			.19
Present	23 (21.3)	63 (30.6)	
Absent	82 (75.9)	133 (64.6)	
Not available	3 (2.8)	10 (4.9)	
Mitotic rate			.78
0	11 (10.2)	17 (8.3)	
$<1/mm^2$	3 (2.8)	5 (2.4)	
$1–10/mm^2$	77 (71.3)	137 (66.5)	
$>10/mm^2$	12 (11.1)	30 (14.6)	
Not available	5 (4.6)	17 (8.3)	
Tumor infiltrating lymphocytes			.90
Brisk	18 (16.7)	32 (15.5)	
Non-brisk	56 (51.9)	110 (53.4)	
Absent	26 (24.1)	43 (20.9)	
Not available	8 (7.4)	21 (10.2)	
Tumor regression			.48
Present	12 (11.1)	29 (14.1)	
Absent	89 (82.4)	156 (75.7)	
Not available	7 (6.5)	21 (10.2)	
Nodal stage			.11
N0	76 (66.7)	157 (70.7)	
N1	18 (15.8)	45 (20.3)	
N2	14 (12.3)	12 (5.4)	
N3	6 (5.3)	8 (3.6)	
Stage groups			.24
0	1 (0.9)	1 (0.5)	
I	47 (41.2)	76 (34.2)	
II	25 (21.9)	71 (32.0)	
III	37 (32.5)	60 (27.0)	
IV	4 (3.5)	11 (5.0)	
Not available	0 (0)	3 (1.4)	

*Three individuals were excluded from the total of 339 patients due to missing indoor tanning data. Staging is based on 8th Edition, American Joint Committee on Cancer Guidelines (11).

†Some percentages do not total 100% due to rounding.

‡Fisher exact test with two-sided P values for the comparison between ever-users and nonusers.

§BRAF mutation status in exon 15 was assessed by real-time polymerase chain reaction utilizing the Qiagen BRAF RGQ PCR Kit. Non-V00E genotype included V600K and V600R.

‖Primary tumor characteristics are analyzed in patients with primary known melanoma.

melanoma (5,7,8,21), and evidence exists for indoor tanning as a cause of melanoma, not a proxy for sun exposure (6,8,12–15,22–26). To address the birth-cohort effect, we divided the patients into those born before and after 1945. In the after-1945 cohort, ever-users were still younger at diagnosis compared with nonusers. Indoor tanning had an independent effect on age at diagnosis after adjusting for sex, skin type, hair color, eye color, sun exposure, family history, and birth before or after 1954 (data not shown). Despite these limitations, our findings add to existing work and begin to reveal, at a pathway level, how indoor tanning may contribute to melanoma development.

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