Extremity nevus count is an independent risk factor for basal cell carcinoma and melanoma, but not squamous cell carcinoma

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Background: The presence of nevi portends an increased risk for melanoma.

Objective: We sought to examine the association between extremity nevus count and the risk of melanoma and keratinocyte cancers.

Methods: We evaluated prospective cohorts of 176,317 women (the Nurses' Health Study, 1986-2012 and the Nurses' Health Study 2, 1989-2013) and 32,383 men (Health Professionals Follow-up Study, 1986-2012). Information on nevus count (none, 1-5, 6-14, ≥15) on the extremity was collected at baseline.

Results: There were 1704 incident cases of melanoma, 2296 incident cases of squamous cell carcinoma, and 30,457 incident cases of basal cell carcinoma, with a total of 4,655,043 person-years for melanoma and 4,267,708 person-years for keratinocyte cancers. The presence of an extremity nevus was associated with an increased risk of melanoma in all anatomic areas and increased risk of basal cell carcinoma (BCC). Individuals with ≥15 nevi had the highest risk of melanoma and BCC compared to those without any extremity nevi (melanoma hazard ratio 2.79 [95% confidence interval 2.04-3.83]; BCC HR 1.40 [95% confidence interval 1.32-1.49]). No significant association was observed for squamous cell carcinoma.

Limitations: Limitations of our study included self-reported nevus count and detection bias.

Conclusions: Extremity nevus count is a helpful clinical marker in risk-stratifying individuals for BCC and melanoma on all body sites. (J Am Acad Dermatol 2019;80:970-8.)

Key words: basal cell carcinoma; melanoma; nevus count; prospective cohort studies; squamous cell carcinoma.

The development of melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) is dependent on a complex interaction between host factors, anatomic sites, and environmental risk factors, particularly the timing, intensity, and duration of sun exposure.

Having an increased number of nevi has been shown to portend an increased risk for melanoma.[1-6] However, the relationship between nevus count and keratinocyte cancers has not been clearly established in population studies, except in limited segments of the population, such as pediatric transplant population, who are at increased risk for both nevi and keratinocyte cancer development.[7]

Self-reported nevus count on extremities can help patients self-stratify skin cancer risk. Our study using the large prospective cohorts of women and men sought to provide refined risk estimates for nevus count and both melanoma and keratinocyte cancers.

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METHODS

Study populations

The study population is comprised of 3 prospective cohorts: the Nurses' Health Study (NHS) (1976), which included 121,700 female nurses, the Health Professionals Follow-Up Study (HPFS) (1986), which included 51,529 male health professionals, and the Nurses' Health Study 2 (NHS2) (1989), which included 116,686 female nurses.

Ascertainment of nevus count

In the NHS, NHS2, and HPFS, participants were asked at inception to provide information on melanocytic nevus count on the left arm and forearm in the NHS (>3 mm diameter), both forearms in the HPFS (> 3 mm diameter), and both lower legs in the NHS2 (without specification of size), choosing from among the following categories: none, 1-2, 3-5, 6-9, 10-14, 15-20, and ≥21. Nevus count on extremities was chosen because tallying the total body nevus count is more time-consuming and has a larger margin of error.[8] Extremity nevus count has been shown to be a reliable proxy for total body nevus count.[9] Having one nevus or more on the extremity is associated with an increased risk of melanoma; the risk increased with higher nevus count, with the highest risk seen in those with ≥10 nevi on the extremities.[10,11]

CAPSULE SUMMARY

- Individuals with high numbers of nevi are at increased risk for melanoma.
- Having any extremity nevi increases risk for basal cell carcinoma and melanoma on all body sites; highest risks are seen in those with 15 or more extremity nevi.

Ascertainment of covariates

Information on body weight and smoking status was collected in the baseline questionnaire and updated in biennial, follow-up questionnaires. A food frequency questionnaire was administered in 1980 for the NHS, in 1991 for the NHS2, and in 1986 for the HPFS and every 4 years thereafter as previously described.[12] Data on the following phenotypic and sun exposure–related factors were also collected via follow-up questionnaires[13,14]: ethnicity, family history of melanoma in first-degree relatives (parents and siblings), natural hair color in early adulthood (age 21 years in women and age 18 years in men), skin reaction to sun exposure ≥2 hours as a child or adolescent, number of lifetime severe sunburns, time spent in direct sunlight per week over different ages, and residential history. Ultraviolet (UV) flux is an estimate of the amount of UVB radiation and the portion of UVA radiation reaching the earth's surface, as measured by a Robertson–Berger meter.[15] UV flux for each study participant is estimated based on residential history according to detailed methods documented previously.[16] Childhood tanning ability (practically none, little, average, or deep tan) was collected for the NHS.

Ascertainment of incident melanoma, basal cell carcinoma, and squamous cell carcinoma

Participants reported new diagnoses of skin cancer (melanoma, SCC, or BCC) biennially. Medical and pathologic reports of melanoma and SCC were collected and manually reviewed by study staff who were blinded to exposure status. For melanoma in situ and SCC in situ, cases were excluded from the analysis to eliminate potential bias (ie, interobserver variability). Validation of BCC diagnosis was performed in subsets within the cohort, with an average of >90% confirmation rate.[17-19] The procedures and protocols of the study were approved by the institutional review board at Brigham and Women's Hospital.

Statistical analysis

Participants contributed person-time from the date of return of the baseline questionnaire until the date of diagnosis of skin cancer, death, or end of follow-up (June 2012 in the NHS, June 2013 in the NHS2, and January 2012 in the HPFS), whichever came first. We excluded those with history of melanoma or keratinocyte cancers at cohort inception. We used Cox proportional hazards regression to estimate the age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the disease outcome associated with nevus count (none, 1-5, 6-14, and ≥15). Multivariable-adjusted analyses were performed adjusting for age (continuous variable), body mass index (<25, 25-29.9, or ≥30 kg/m^2), smoking (never, past, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/day), childhood reaction to ≥2 hours of sun as a child or adolescent (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan [the NHS only]), number of lifetime severe sunburns (0, 1-2, 3-5, 6-9, or ≥10), hair color (red, blonde, light brown, dark brown, or black), family history of melanoma in a first-degree relative (yes or no), citrus consumption (<2 times/week, ≥2 to ≤4 times/week, >4 times/week to <1 time/day, or ≥1 time/

Abbreviations used:

BCC: basal cell carcinoma
CI: confidence interval
HPFS: Health Professionals Follow-up Study
HR: hazard ratio
NHS: Nurses' Health Study
NHS2: Nurses' Health Study 2
SCC: squamous cell carcinoma
UV: ultraviolet

day), average sun exposure per week (<1, 2-5, 6-10, or ≥11 hours), and ambient UV flux (in tertiles). Potential confounding factors included in the multivariable-adjusted model were selected based on our previous knowledge. For example, citrus consumption was controlled for the multivariate analysis given that citrus consumption was found to be associated with an increased risk of malignant melanoma[20] and keratinocyte cancers[21] within our cohorts, which was believed to be related to photocarcinogenic properties of psoralen within citrus fruits.

We performed trend tests across nevus count categories by assigning median values for these categories and treating the new variables as continuous terms in the models. No heterogeneity of the associations was found between cohorts ($P > .05$) using the Q statistic.[22] We performed a meta-analysis for NHS, NHS2, and HPFS combined data using a random effects model to pool the HRs from the cohorts. We used SAS software (version 9.4; SAS Institute, Inc., Cary, NC) for all statistical analyses. All statistical tests were 2-tailed, and the significance level was set at $P < .05$.

RESULTS

During the follow-up of 176,317 women (74,241 from the NHS between 1986-2012 with 1,738,599 person-years for melanoma and 1,538,042 person-years for keratinocyte cancers; 102,076 from the NHS2 between 1989-2013 with 2,211,581 person-years for melanoma and 2,128,147 person-years for keratinocyte cancers) and 32,383 men (from the HPFS, 1986-2012, 704,863 person-years for melanoma and 601,519 person-years for keratinocyte cancers), we documented 1704 incident cases of melanoma, 2296 incident cases of SCC, and 30,457 incident cases of BCC.

Baseline characteristics

Baseline characteristics among individuals in each nevus count group are shown in Table I.

Nevus count and risk of incident melanoma

Table II shows the age- and multivariable-adjusted risk of melanoma in each nevus count group. In all 3 cohorts, compared with those with no nevi on the extremity, there is an increase in risk of incident melanoma in individuals with ≥1 nevi in a dose-dependent trend (P for trend <.0001); having any nevus on the extremity is associated with a significant increased risk of melanoma, with the greatest melanomas risks seen in individuals with 6 to 14 and ≥15 nevi on the extremity. In the combined analysis, individuals with 6 to 14 nevi or ≥15 nevi on the extremity had multivariable-adjusted HRs of 2.76 (95% CI 2.16-3.53) and 2.79 (95% CI 2.04-3.83), respectively.

Nevus count and risk of incident melanoma by anatomic site

Figure 1 shows that in the combined analysis, an association was seen between nevus count and melanomas at all anatomic sites, which became stronger with higher nevus count (P for trend of <.0001).

Nevus count and risk of incident keratinocyte cancers

Tables III and IV show the age- and multivariable-adjusted risk of SCC and BCC in each nevi group, respectively. No statistically significant association between nevus count and SCC was observed (Table III). In contrast, for BCC, age- and multivariable-adjusted hazard ratios were higher across all nevi groups (Table IV) in a dose-dependent manner (P for trend <.0001). Having any nevus on the extremity carried an increase in BCC risk; individuals with ≥15 nevi had a 40% elevated likelihood of BCC relative to individuals without any nevi on the extremity (multivariable-adjusted HR 1.40 [95% CI 1.32-1.49]).

Considering that we fitted both age- and multivariable-adjusted models for the associations between nevus count and 3 types of skin cancer in 3 independent cohorts, we used Bonferroni correction to correct for multiple comparison; the adjusted significance level of P value was .05/18 (2 models*3 outcomes*3 cohorts; .0027). The association patterns remained the same after multiple comparison correction (ie, nevus count was significantly associated with risk of melanoma and BCC, but not SCC). In addition, considering the small number of individuals with ≥15 nevi, we also conducted a sensitivity analysis by collapsing the "6 to 14" and "≥15" nevus count levels. The results were consistent with those of the primary analyses.

Table I. Age-adjusted baseline characteristics according to categories of nevus count in the NHS (1986), NHS2 (1989), and HPFS (1986): Association between nevus count and risk of incident basal cell carcinoma

	NHS nevus count				NHS2 nevus count				HPFS nevus count			
Characteristic	None (n = 47,000)	1-5 (n = 23,844)	6-14 (n = 2740)	≥15 (n = 657)	None (n = 50,712)	1-5 (n = 29,586)	6-14 (n = 12,205)	≥15 (n = 9573)	None (n = 21,807)	1-5 (n = 8832)	6-14 (n = 1352)	≥15 (n = 392)
Mean age, y (SD)	52.7 (7.2)	51.9 (7.1)	51.8 (7.1)	51.9 (7.2)	35.8 (4.7)	35.9 (4.6)	35.9 (4.7)	35.8 (4.6)	54.4 (9.9)	54.6 (9.8)	55.7 (9.8)	56.4 (9.9)
Mean body mass index, kg/m^2 (SD)	25.2 (4.7)	25.6 (5.0)	26.6 (5.6)	26.8 (5.6)	24.3 (5.2)	24.1 (5.1)	23.8 (4.7)	23.5 (4.5)	24.8 (4.6)	24.9 (4.6)	25.2 (4.6)	25.3 (4.9)
Current smoker, %	22.4	20.4	19.9	20.1	8.9	8.4	8.2	8	9.2	8.1	8	9.4
Mean alcohol intake, gram/week (SD)	6.3 (10.9)	6.0 (10.4)	5.7 (9.8)	5.1 (8.8)	3.2 (6.1)	3.1 (6.0)	3.1 (5.9)	3.3 (6.4)	11.8 (15.8)	11.6 (15.4)	11.4 (15.3)	11.3 (16.4)
Mean citrus consumption, times/week (SD)	0.9 (0.8)	0.9 (0.8)	0.9 (0.9)	0.9 (0.8)	0.6 (0.6)	0.6 (0.6)	0.6 (0.6)	0.6 (0.6)	1.0 (0.9)	1.0 (0.9)	1.0 (0.8)	1.0 (0.9)
Family history of melanoma, %	2.6	3	3.3	2.6	3.9	4.4	5.2	5.9	3.3	4.2	4.6	4.8
Red/blond hair color, %	15.5	15.8	14.9	13.8	19.7	21.4	20.8	22.3	13.9	14.4	13.3	11.2
Burn/painful burn/blister reaction to ≥2 hours of sun exposure as a child/adolescent, %	35.1	37.6	42.4	41.2	48.3	48	47.8	51.8	69.4	73.2	77.4	74.4
Average/deep tan after repeated sun exposure as a child/adolescent, %	70.1	69	66.6	66.3	-	-	-	-	-	-	-	-
No. of lifetime sunburns ≥6, %	54.1	58.8	66.2	66.5	9.2	9.9	10.9	13.1	34.9	34.9	39.8	43.5
Average sun exposure ≥6 hours per week, %	40.1	41.4	44.2	41.4	43.3	42.3	42.6	45.3	68.1	66.7	68.3	69.6
Mean annual UV flux, mW/m^2 (SD)	188.9 (29.2)	189.0 (29.5)	188.2 (29.5)	189.2 (29.7)	170.1 (36.0)	172.1 (36.6)	172.6 (36.6)	175.2 (38.3)	191.8 (27.6)	192.6 (27.9)	193.9 (28.7)	193.0 (27.8)

Values are standardized to the age distribution of the study population. The NHS assessed the left arm and left forearm, the HPFS assessed the left and right forearms, and the NHS2 assessed the left and right lower legs.

HPFS, Health Professionals Follow-up Study; *NHS*, Nurses' Health Study; *NHS2*, Nurses' Health Study 2; *SD*, standard deviation; *UV*, ultraviolet.

Table II. Association between nevus count and risk of incident melanoma

	Person-years	Cases	Crude incidence rates (cases/100,000 person-years)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR* (95% CI)
NHS					
None	109,9613	321	29.19	1.00	1.00
1-5	560,140	304	54.27	1.87 (1.60-2.19)	1.81 (1.54-2.12)
6-14	63,675	68	106.79	3.70 (2.85-4.81)	3.50 (2.69-4.55)
≥15	15,170	11	72.51	2.55 (1.40-4.65)	2.45 (1.34-4.48)
P for trend				<.0001	<.0001
NHS2					
None	1,100,206	154	14.00	1.00	1.00
1-5	641,808	132	20.57	1.46 (1.16-1.85)	1.42 (1.13-1.80)
6-14	263,795	94	35.63	2.54 (1.96-3.28)	2.43 (1.88-3.15)
≥15	205,773	105	51.03	3.65 (2.85-4.68)	3.31 (2.58-4.25)
P for trend				<.0001	<.0001
HPFS					
None	475,925	277	58.20	1.00	1.00
1-5	192,062	184	95.80	1.63 (1.35-1.97)	1.59 (1.32-1.92)
6-14	28,614	44	153.77	2.61 (1.90-3.59)	2.42 (1.76-3.34)
≥15	8262	10	121.04	2.01 (1.07-3.77)	1.93 (1.02-3.63)
P for trend				<.0001	<.0001
Meta-analysis					
None	2,675,744	752	28.10	1.00	1.00
1-5	1,394,010	620	44.48	1.68 (1.46-1.93)	1.63 (1.43-1.86)
6-14	356,084	206	57.85	2.92 (2.28-3.74)	2.76 (2.16-3.53)
≥15	229,205	126	54.97	2.91 (2.01-4.22)	2.79 (2.04-3.83)
P for trend				<.0001	<.0001

CI, Confidence interval; *HPFS*, Health Professionals Follow-up Study; *HR*, hazard ratio; *NHS*, Nurses' Health Study; *NHS2*, Nurses' Health Study 2.

*Multivariable-adjusted models were adjusted for age (continuous variable), body mass index (<25, 25-29.9, or ≥30 kg/m^2), smoking (never, past, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/day), childhood reaction to ≥2 hours of sun (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan [NHS only]), number of lifetime severe sunburns (0, 1-2, 3-5, 6-9, or ≥10), hair color (red, blonde, light brown, dark brown, or black), family history of melanoma in first-degree relative (yes or no), citrus consumption (<2 times/week, ≥2 to ≤4 times/week, >4 times/week to <1 time/day, or ≥1 time/day), average sun exposure per week (<1, 2-5, 6-10, or ≥11 hours), and ambient ultraviolet flux (in tertiles).

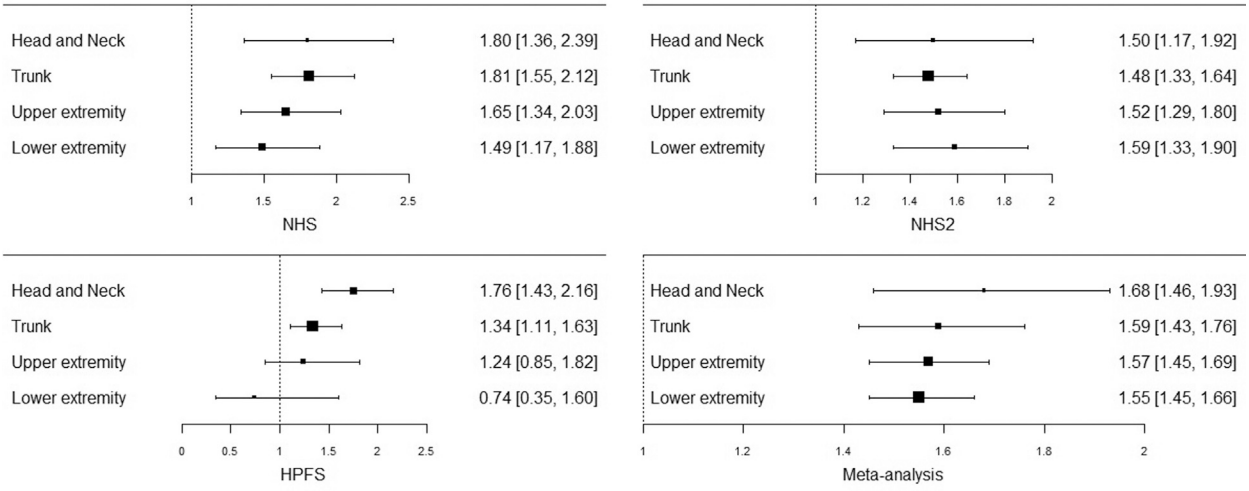

Fig 1. Nevus count and risk of incident melanoma by anatomic site. R's plot function of association between per 5-count increase in nevus count and risk of incident melanoma by anatomic site.

Table III. Association between nevus count and risk of incident squamous cell carcinoma

	Person-years	Cases	Crude incidence rates (cases/100,000 person-years)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR* (95% CI)
NHS					
None	980,178	822	83.86	1.00	1.00
1-5	490,114	445	90.80	1.11 (0.99-1.25)	1.08 (0.96-1.21)
6-14	54,919	63	114.71	1.43 (1.10-1.84)	1.40 (1.08-1.81)
≥15	12,832	13	101.31	1.26 (0.73-2.18)	1.19 (0.69-2.07)
P for trend				.003	.012
NHS2					
None	1,061,953	260	24.48	1.00	1.00
1-5	617,425	145	23.48	0.95 (0.77-1.16)	0.93 (0.76-1.14)
6-14	253,173	57	22.51	0.92 (0.69-1.22)	0.88 (0.66-1.17)
≥15	195,596	44	22.50	0.93 (0.67-1.27)	0.82 (0.60-1.13)
P for trend				.511	.175
HPFS					
None	409,379	290	70.84	1.00	1.00
1-5	161,176	130	80.66	1.13 (0.92-1.39)	1.12 (0.91-1.37)
6-14	24,035	21	87.37	1.19 (0.76-1.85)	1.14 (0.73-1.77)
≥15	6929	6	86.59	1.11 (0.50-2.50)	1.02 (0.45-2.31)
P for trend				.265	.399
Meta-analysis					
None	2,451,510	1372	55.97	1.00	1.00
1-5	1,268,715	720	56.75	1.08 (0.99-1.18)	1.05 (0.96-1.15)
6-14	332,127	141	42.45	1.16 (0.87-1.56)	1.11 (0.82-1.52)
≥15	215,357	63	29.25	1.01 (0.78-1.31)	0.92 (0.70-1.19)
P for trend				.284	.541

CI, Confidence interval; *HPFS*, Health Professionals Follow-up Study; *HR*, hazard ratio; *NHS*, Nurses' Health Study; *NHS2*, Nurses' Health Study 2.

*Multivariable-adjusted models were adjusted for age (continuous variable), body mass index (<25, 25-29.9, or ≥30 kg/m^2), smoking (never, past, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/day), childhood reaction to ≥2 hours of sun (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan [NHS only]), number of lifetime severe sunburns (0, 1-2, 3-5, 6-9, or ≥10), hair color (red, blonde, light brown, dark brown, or black), family history of melanoma in first-degree relative (yes or no), citrus consumption (<2 times/week, ≥2 to ≤4 times/week, >4 times/week to <1 time/day, or ≥1 time/day), average sun exposure per week (<1, 2-5, 6-10, or ≥11 hours), and ambient ultraviolet flux (in tertiles).

DISCUSSION

Our study reveals several interesting findings. First, we found that nevus count was independently associated with melanoma on all anatomic sites. Second, we observed in this study that nevus count is associated with BCC in a dose-dependent manner.

Nevus cells are thought to arise from the proliferation of genetically altered melanocytes.[23] Host factors such as fair skin,[24-27] freckling of the face,[24-28] tendency to burn in the sun,[25,28] and family history of high nevus count[24] have been well documented as being associated with higher nevus count in children. However, the exact triggers for nevus development are less well defined.

Similar to melanoma from intermittently sun-exposed skin, a BRAF mutation has been detected in congenital nevi and common acquired nevi at sun-exposed sites.[29] However, the relationship between UV radiation and nevi development may not be as straightforward as it appears, as melanocytes from different anatomic sites may have distinct responses to mitogenic stimuli.[30] The timing of UV radiation was also previously thought to be critical. Early life intense UV radiation or sunburns was thought to be the primary inciting event in the development of common acquired nevi.[31-33] However, recent studies show that chronic cumulative sun exposure, such as ambient sun exposure from living at high latitudes, may also be a risk factor for nevi development in children.[6,24,26,34-36] In addition, there is evidence that truncal melanomas are more strongly associated with nevus count than melanoma on chronically sun-damaged skin.[5] However, our study revealed that having nevus on the extremity is independently associated with all anatomic sites in the combined analysis, suggesting that extremity nevus count may be a good predictor for risk of development of melanoma overall.

Table IV. Association between nevus count and risk of incident basal cell carcinoma

	Person-years	Cases	Crude incidence rates (cases/ 100,000 person-years)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR* (95% CI)
NHS					
None	980,178	9157	934.22	1.00	1.00
1-5	490,114	5340	1089.54	1.19 (1.15-1.24)	1.16 (1.12-1.20)
6-14	54,919	659	1199.95	1.34 (1.24-1.45)	1.29 (1.19-1.40)
≥15	12,832	175	1363.78	1.53 (1.32-1.78)	1.46 (1.25-1.69)
P for trend				<.0001	<.0001
NHS2					
None	1,061,953	3517	331.18	1.00	1.00
1-5	617,425	2276	368.63	1.11 (1.05-1.17)	1.09 (1.03-1.14)
6-14	253,173	1027	405.65	1.23 (1.14-1.31)	1.18 (1.10-1.26)
≥15	195,596	1004	513.30	1.56 (1.45-1.67)	1.41 (1.32-1.51)
P for trend				<.0001	<.0001
HPFS					
None	409,379	4712	1151.01	1.00	1.00
1-5	161,176	2175	1349.46	1.17 (1.11-1.23)	1.15 (1.10-1.21)
6-14	24,035	307	1277.30	1.08 (0.96-1.21)	1.04 (0.93-1.17)
≥15	6929	108	1558.67	1.32 (1.09-1.60)	1.26 (1.04-1.53)
P for trend				<.0001	.0008
Meta-analysis					
None	2,451,510	17,386	709.20	1.00	1.00
1-5	1,268,715	9791	771.73	1.16 (1.11-1.21)	1.14 (1.09-1.18)
6-14	332,127	1993	600.07	1.22 (1.09-1.36)	1.17 (1.06-1.31)
≥15	215,357	1287	597.61	1.51 (1.40-1.64)	1.40 (1.32-1.49)
P for trend				<.0001	<.0001

CI, Confidence interval; *HPFS*, Health Professionals Follow-up Study; *HR*, hazard ratio; *NHS*, Nurses' Health Study; *NHS2*, Nurses' Health Study 2.

*Multivariable-adjusted models were adjusted for age (continuous variable), body mass index (<25, 25-29.9, or ≥30 kg/m^2), smoking (never, past, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/day), childhood reaction to ≥2 hours of sun (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan [NHS only]), number of lifetime severe sunburns (0, 1-2, 3-5, 6-9, or ≥10), hair color (red, blonde, light brown, dark brown, or black), family history of melanoma in first-degree relative (yes or no), citrus consumption (<2 times/week, ≥2 to ≤4 times/week, >4 times/week to <1 time/day, or ≥1 time/day), average sun exposure per week (<1, 2-5, 6-10, or ≥11 hours), and ambient ultraviolet flux (in tertiles).

In this study, we also found that higher nevus count is an indicator of increased risk for BCC development, independent of host and environmental risk factors, suggesting that there are likely currently unknown shared risk factors in the generation of nevi and BCC. BCC arises from the basal cell layer of the epidermis in hair-bearing skin.[23] Melanocytes, including those thought to be precursors to nevus cells, reside in the same layer of the skin as these basal keratinocytes.[23] BCC is most commonly associated with intense, intermittent sun exposure.[37,38] However, studies have suggested that BCCs (particularly nodular BCCs) may be related to chronic sun exposure.[39,40] Interestingly, both nonpigmented and pigmented BCCs have melanocytes in the basal layers of the tumor and within the tumor,[41] with varying degrees of melanin; pigmented BCCs have more melanocytes than nonpigmented BCCs.[41] The presence of melanocytes or melanin in BCCs point to the possibility that the same mitogenic pathway that induces BCC development also promotes melanocyte proliferation and melanogenesis. Indeed, melanogenesis occurs in the setting of UV exposure and DNA damage.[42] Melanin, particularly eumelanin, is believed to be an effective light absorber and protective against UV damage.[43] Individuals who are unable to adequately generate inducible pigmentation or who have a lower percentage of eumelanin may require higher amounts of melanocyte-activating factors, inducing generation of nevi, and are less likely to protect the basal layer of the skin from the mitogenic effects of UV radiation against development of BCC. Nevi may be viewed as the reaction of melanocytes in the skin of susceptible individuals to UV radiation, and these are the same individuals who develop BCCs.

In this study, we did not find a compelling association between nevus count and SCC development. SCC arises from keratinocytes in the upper layers of the epidermis, away from the basal layer where basal

keratinocytes and melanocytes reside. SCC is associated with chronic sun exposure,[38,44,45] as opposed to BCCs and nevi, which are generally believed to be associated with intermittent sun exposure. We know from clinical practice that patients of all phenotypes can develop SCC. Indeed, SCC encompasses a much more diverse group of tumors that are biologically and behaviorally distinct from BCC. While similar to melanoma and BCC, SCC development is associated not only with lifetime cumulative sun exposure,[44,45] light phototype,[46] and immunosuppression[46,47]; SCCs are also associated with chronic wounds/burns[48] and human papillomavirus infection.[49,50] From a statistical perspective, these results can also be viewed as a sensitivity analysis of the degree of effect size between nevi and skin cancer risk; while a weak (ie, less clinically meaningful) association between nevi and SCC may exist, the association is too small to be detected given the relatively small number of cases of SCC in these cohorts compared with BCC.

One limitation of this study is that nevus count was self-reported; however, the genetic analysis using self-reported nevus count as outcome identified a previously reported nevus-related gene[51,52] as well as newly uncovered melanoma risk factors.[53,54] Another limitation is detection bias. Patients who have high number of nevi may be screened more frequently than patients with fewer nevi. Despite these limitations, these results, based on 3 high-quality cohort databases that allowed for the control of a comprehensive list of confounders, confirm the previously known association between nevi and melanoma as an internal validation. In addition, this study adds unique insight into the association between nevi and anatomic-specific melanoma development and risk of keratinocyte cancers.

In conclusion, based on the results of this study, extremity nevus count serves as skin's convenient marker for risk-stratifying individuals for melanoma and BCC. Providers should be aware of these increased risks in patients with any nevi on the extremity, with special attention to those with ≥15 extremity nevi.

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