Having a first-degree relative with melanoma increases lifetime risk of melanoma, squamous cell carcinoma, and basal cell carcinoma

Erin X. Wei, MD,[a] Xin Li, ScD,[b] and Hongmei Nan, PhD[b,c]
Boston, Massachusetts, and Indianapolis, Indiana

Background: Previous studies have found familial aggregation of melanoma and keratinocyte cancers (KCs).

Objective: We sought to determine the risk of melanoma and KCs in those with a positive family history of melanoma while controlling for pigmentary and environmental risk factors.

Methods: We prospectively followed 216,115 participants from the Nurses' Health Study, Nurse's Health Study 2, and Health Professionals Follow-up Study for more than 20 years. Cox proportional hazards regression controlling for known risk factors for skin cancer was used to estimate association between family history of melanoma and melanoma and KCs.

Results: Compared with those without a family history of melanoma, individuals with a family history of melanoma had a 74% increased risk of melanoma (hazard ratio [HR], 1.74; 95% confidence interval [CI], 1.45-2.09), a 22% increased risk of squamous cell carcinoma (HR, 1.22; 95% CI, 1.06-1.40), and a 27% increased risk of basal cell carcinoma (HR, 1.27; 95% CI, 1.12-1.44). Family history of melanoma increased the risk of development of truncal melanoma in both sexes, extremity melanoma in women, and extremity squamous cell carcinoma in women.

Limitations: Limitations of this study include self-reported family history and detection bias.

Conclusion: Individuals with a family history of melanoma are at an increased risk of melanoma and KCs. (J Am Acad Dermatol 2019;81:489-99.)

Key words: basal cell carcinoma; family history of melanoma; keratinocyte cancers; melanoma; prospective cohort studies; risk factor; skin cancer; squamous cell carcinoma.

The 3 most common forms of skin cancers include keratinocyte cancers (KCs) (ie, squamous cell carcinoma [SCC] and basal cell carcinoma [BCC]), and melanoma.[1] It is known that family history of melanoma increases individual risk of melanomas,[2-6] though the magnitude of the association between family history of melanoma and melanoma risk has varied among studies. Some have reported familial aggregation of melanoma and KCs.[7] Indeed, there are several shared intrinsic and

From Brigham and Women's Hospital, Harvard Medical School, Boston,[a] and Department of Epidemiology, Richard M. Fairbanks School of Public Health,[b] and IU Melvin and Bren Simon Cancer Center, Indiana University, Indianapolis.[c]
Dr Wei and Dr Li contributed equally to this article.
Funding sources: Supported in part by the National Institutes of Health (grants UM1 CA186107, P01 CA87969, UM1 CA176726, UM1 CA167552, and R01 CA137365). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funding source had no role in the design of the study, data collection, analysis, interpretation of the data, manuscript writing, or decision to submit the manuscript for publication.
Conflicts of interest: None disclose.
The authors had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.
Accepted for publication April 14, 2019.
Reprint requests: Hongmei Nan, PhD, Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University; R3-C216A, 980 West Walnut St, Indianapolis, IN 46202. E-mail: hnan@iu.edu.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2019.04.044

extrinsic risk factors for all 3 types of skin cancers. The most important shared risk factors for development of melanoma and KCs is ultraviolet radiation (UVR), directly via UVR-induced DNA damage and indirectly through UVR-induced immunosuppression.[6] Further, intrinsic factors such as variation in pigmentary genes[8,9] and nonpigmentary genes[10-15] have been found to increase risk of both melanoma and KCs. Other genes implicated in increased familial risk of melanoma have also been found in sporadic KCs.[16-23]

Despite the suspected link between all 3 skin cancers, little is known on a population scale regarding whether individuals with a family history of melanomas are also at risk of KCs. A single, registry-based study suggesting an increased risk of SCC in individuals with a family history of melanoma[24] is limited by the lack of data on individual pigmentary and environmental risk factors. The study found that the relative risk of SCC increased from 1.46 (95% confidence interval [CI], 1.37-1.56) with a single family member with melanoma to 2.39 (95% CI, 1.29-4.38) when 2 or more family members had melanoma or when a family member had multiple melanomas.[24] Another study based on data from the Nurses' Health Study (NHS) that found increased risk of BCC (relative risk, 1.37; 95% CI, 1.27-1.49) in individuals with a family history of melanoma[25] is limited by the lack of male counterparts. There is also strong evidence that familial propensity for melanoma has a strong anatomic preference,[26-30] which has not been evaluated for KCs.

This study sought to evaluate whether family history of melanoma in a first-degree relative heralds increased risk of melanoma and KCs among white participants from 3 large prospective cohorts of both US men and US women, as well as to evaluate whether the association with melanoma and SCC is site dependent. Additionally, this study assessed the proportions of association explained by intrinsic and extrinsic factors by controlling for a wide array of known risk factors for skin cancer.

CAPSULE SUMMARY

- Individuals with a family history of melanoma are at increased risk of melanoma.
- This study revealed that the trunk and extremities are both melanoma-prone sites in individuals with a family history of melanoma; these individuals are also at an increased risk of basal cell carcinoma and extremity squamous cell carcinoma.

MATERIALS AND METHODS

Populations, outcome, and covariate ascertainment

The NHS was established in 1976 with 121,700 female nurses aged 30 to 55 years. The Health Professionals Follow-Up Study (HPFS) began in 1986 with 51,529 male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians aged 40 to 75 years. The Nurses' Health Study 2 (NHS2) began in 1989 with 116,686 nurses between the ages of 25 and 42 years.

In the NHS, NHS2, and HPFS, participants were asked in questionnaires to provide information on family history of melanoma in first-degree relatives (parents and siblings). Self-reported outcomes from these cohorts have been validated, reflecting a high degree of health literacy.[31,32] For the NHS, family history of melanoma was asked in 1982 and updated in 1992, 1996, 2000, and 2008. For the NHS2, family history of melanoma was asked in 1989 and updated in 1997, 2001, and 2005. In the HPFS, family history of melanoma was asked in 1990 and updated in 1992 and 2008.

Participants reported new diagnoses of skin cancer (melanoma, SCC, or BCC) biennially. Medical and pathologic reports were collected from participant reports of melanoma or SCC, which were then reviewed by study physicians (who were unaware of exposure status) to retrieve information on tumor histology. Anatomic locations for melanoma and SCC were collected from the pathology reports and medical records; anatomic information on BCC was not collected. High accuracy of self-reported BCC among subsets of cohort participants has been demonstrated in previous validation studies, with approximately 90% of cases confirmed by histopathologic findings or medical records.[31,33,34] For melanoma and SCC, in situ cases were excluded from this analysis. The procedures and protocols of the study were approved by the institutional review boards at Brigham and Women's Hospital (1999-P-011114).

Information on body weight and smoking status was initially collected in the baseline questionnaire and repeatedly collected and updated through biennial questionnaires. A 130-item semiquantitative food frequency questionnaire was administered at the baseline year of the current analysis (for the NHS, 1986; for the NHS2, 1989; and for the HPFS, 1986)[35] and every 4 years thereafter. We calculated total alcohol intake in grams per day by using methods previously described.[36] Citrus consumption was calculated as the sum of the individual products by using methods previously described.[37,38] Citrus consumption was included given that it was found to be

Abbreviations used:

BCC: basal cell carcinoma
BMI: body mass index
CI: confidence interval
HPFS: Health Professionals Follow-Up Study
KC: keratinocyte cancer
NHS: Nurses' Health Study
NHS2: Nurses' Health Study 2
SCC: squamous cell carcinoma
UV: ultraviolet
UVR: ultraviolet radiation

associated with melanoma as well as with KCs in our cohort population.[37,38] The hypothesis was that psoralen or other ingredients of citrus fruits act as direct photosensitizers/carcinogens.

In 1980s, participants were asked to provide information on mole count (>3 mm in diameter) on the extremity. Data on the following phenotypic and sun exposure–related factors were also collected via follow-up questionnaires[25,39]: natural hair color in early adulthood (age 21 years in women and age 18 years in men), skin reaction to sun exposure of 2 hours or longer as a child or adolescent, number of severe lifetime sunburns, time spent in direct sunlight per week over different ages, and residential history. Cumulative ultraviolet (UV) flux for each study participant was estimated on the basis of residential history according to detailed methods documented previously.[40] Childhood tanning ability (practically none, little, average, or deep tan) was collected for the NHS only.

Statistical analysis

We excluded participants who did not report their date of birth and those of nonwhite ancestry. People who had baseline cancers or died during follow-up were excluded.

Participants contributed person-time from 1986 for the NHS and the HPFS, and 1989 for the NHS2 until the date of diagnosis of skin cancer, death, or end of follow-up (June 2012 in the NHS, June 2013 in the NHS2, January 2012 in the HPFS), whichever came first. A Cox proportional hazards regression model was used to estimate the age-adjusted (model 1) and multivariable-adjusted (models 2-5) hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the disease outcome associated with a family history of melanoma. To determine how much of the association with melanoma family history is explained by UV-related factors, we fitted multiple MV models by including different sets of covariates of interest: model 1-adjusted for age only; model 2-adjusted for non–UV-related host and environmental characteristics only (age, body mass index [BMI], smoking, and citrus consumption); model 3-adjusted for factors adjusted for in model 2, as well as for intrinsic UV-related factors (hair color, childhood reaction to sun, childhood tanning ability, and mole count); model 4-adjusted for factors adjusted for in model 2, as well as for extrinsic UV-related factors (number of sunburns, average sun exposure, and ambient UV flux), and model 5-adjusted for all potential confounding factors collected in the cohorts. We also performed a meta-analysis for the NHS, NHS2, and HPFS combined data by using a random-effects model to pool the HRs from the cohorts. We tested heterogeneity between cohorts by using the Q statistic[41]; there was no heterogeneity of the associations found between cohorts ($P > .05$). We used SAS software (version 9, 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 190,345 women, including 84,467 individuals from the NHS (1986-2012), 105,878 individuals from the NHS2 (1989-2013), and 25,770 men from HPFS (1986-2012), we had 1,971,121 person-years of data for melanoma and 1,749,131 person-years of data for KCs from the NHS, 2,292,264 person-years of data for melanoma and 2,205,425 person-years of data for KCs from the NHS2, and 541,241 person-years of data for melanoma and 464,208 person-years for KCs from the HPFS. There were a total of 1688 incident cases of melanoma, 2905 incident cases of SCC, and 30,613 incident cases of BCC.

Baseline characteristics

The age-adjusted baseline characteristics for the NHS, NHS2, and HPFS are shown in Table I. Distribution of baseline characteristics (age, BMI, current smoker, alcohol and citrus consumption, natural red or blond hair color, burn/painful burn/blister reaction to 2 hours or more of sun exposure as a child/adolescent, no/little tan after repeated sun exposure as a child/adolescent, having 6 or more lifetime sunburns, average sun exposure of 6 hours or longer per week, having 1 or more moles on the extremity, and ambient UV flux) were similar between those with and those without a family history of melanoma.

Family history of melanoma and risk of incident melanoma

Table II shows the association between family history of melanoma and the risk of melanoma. In the age-adjusted models (model 1 in Table II), having a family history of melanoma was significantly associated with an increased risk of melanoma

Table I. Age-adjusted baseline characteristics according to family history of melanoma in the NHS, NHS2, and HPFS

Characteristic	NHS		NHS2		HPFS	
	No FHx (n = 82,149)	With FHx (n = 2318)	No FHx (n = 101,251)	With FHx (n = 4627)	No FHx (n = 24,978)	With FHx (n = 792)
Mean age, y (SD)*	52.3 (7.2)	52.6 (7.2)	35.9 (4.7)	35.9 (4.7)	54.6 (9.9)	53.9 (9.7)
Mean BMI, kg/m^2 (SD)	25.3 (4.8)	25.7 (5.1)	24.1 (5.0)	24.2 (5.2)	25.0 (5.1)	25.0 (4.5)
Current smoker, %	21.5	19.7	8.6	9.5	9.7	7.7
Mean alcohol intake, g/wk (SD)	6.2 (10.7)	6.3 (10.8)	3.1 (6.1)	3.4 (6.5)	11.4 (15.5)	11.5 (15.3)
Mean citrus consumption, times/wk (SD)	0.9 (0.8)	0.9 (0.8)	0.6 (0.6)	0.6 (0.6)	1.0 (0.9)	0.9 (0.8)
Red/blond hair, %	15.5	15.2	20.4	24.3	13.6	15.1
Burn/painful burn/blister reaction to ≥2 h of sun exposure as a child/adolescent, %	36.2	40.7	48.2	56.1	70.7	74.5
No/little tan after repeated sun exposure as a child/adolescent, %	30.6	31.8	—	—	—	—
History of ≥6 lifetime sunburns, %	55.8	59.2	9.8	14.3	34.9	37.8
Average sun exposure ≥6 h/wk, %	40.6	41.8	42.9	46.7	66.3	67.1
Having ≥1 mole on the extremity, %	36.8	41.1	50.1	55.8	33.8	39.8
Mean ambient UV flux, mW/m^2 (SD)	188.7 (29.2)	188.7 (28.8)	171.3 (36.4)	174.5 (37.9)	191.2 (27.6)	191.9 (28.1)

Values are standardized to the age distribution of the study population.
BMI, Body mass index; *FHx*, family history of melanoma; *HPFS*, Health Professionals Follow-Up Study; *NHS*, Nurses' Health Study; *NHS2*, Nurses' Health Study 2; *SD*, standard deviation; *UV*, ultraviolet.
*Value is not age-adjusted.

in all 3 cohorts; the associations were not materially changed in the multivariable-adjusted models (models 2-5). There was no significant heterogeneity found among the 3 cohorts. In the combined meta-analysis of the 3 cohorts, individuals with a family history of melanoma had a 74% higher risk of melanoma compared with individuals who reported no family history of melanoma, with a full multivariable-adjusted HR of 1.74 (95% CI, 1.45-2.09) (model 5). To determine how much of the association with melanoma family history is explained by distinct UV-related factors, we additionally conducted multivariable-adjusted models by including different sets of covariates. We found that additionally controlling for intrinsic UV-related covariates, including hair color, childhood reaction to sun, childhood tanning ability, and mole count, resulted in a greater change in magnitude of HRs (HR, 1.79 in model 3 vs 1.93 in model 2 [a 7.3% difference]) compared with the change caused by further adjusting for extrinsic UV-related factors, including number of sunburns, average sun exposure, and ambient UV flux (HR, 1.85 in model 4 vs 1.93 in model 2 [a 4.1% difference]). This suggests that intrinsic UV-related factors explain a higher proportion of the association between family history of melanoma and risk of melanoma than is explained by the extrinsic variables.

Family history of melanoma and melanoma risk by anatomic site

Table III show the association between family history of melanoma and risk of incident melanoma by anatomic site. Trunk was defined as the shoulder, upper and lower back, abdomen, hip, thigh, and buttock. Extremities included both the upper and lower extremities. In the meta-analysis, an association was observed between family history of melanoma and risk of melanomas on the trunk and extremities, with a 94% increase in risk of melanomas on the trunk (HR, 1.94; 95% CI, 1.59-2.36) and an 83% increase for melanomas on the extremities (HR, 1.83; 95% CI, 1.57-2.14).

Family history of melanoma and risk of incident SCC

Table IV shows the association between family history of melanoma and risk of SCC. The proportion explained by intrinsic UV-related factors (HR, 1.25 in model 3 vs 1.31 in model 2 [a 4.6% difference]) was

Table II. HRs (95% CIs) for the association between family history of melanoma and risk of incident melanoma

FHx	Person-years	Cases	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)	Model 5 HR (95% CI)
NHS							
No FHx	1,859,753	695	1.00	1.00	1.00	1.00	1.00
With FHx	111,368	98	2.16 (1.75-2.68)	2.11 (1.71-2.62)	1.98 (1.60-2.45)	2.06 (1.67-2.55)	1.97 (1.59-2.44)
NHS2							
No FHx	2,102,677	428	1.00	1.00	1.00	1.00	1.00
With FHx	189,587	71	2.00 (1.55-2.57)	1.93 (1.50-2.49)	1.72 (1.33-2.22)	1.81 (1.40-2.34)	1.66 (1.29-2.15)
HPFS							
No FHx	518,214	371	1.00	1.00	1.00	1.00	1.00
With FHx	23,027	25	1.50 (1.00-2.25)	1.47 (0.98-2.20)	1.41 (0.94-2.12)	1.44 (0.96-2.16)	1.38 (0.91-2.07)
Meta-analysis							
No FHx	4,480,644	1494	1.00	1.00	1.00	1.00	1.00
With FHx	323,982	194	1.98 (1.66-2.35)	1.93 (1.62-2.29)	1.79 (1.52-2.11)	1.85 (1.56-2.21)	1.74 (1.45-2.09)

Model 1, age-adjusted model; model 2, multivariable-adjusted model adjusting for age (continuous variable), body mass index (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), and citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d); model 3, multivariable-adjusted model adjusting for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d), hair color (red, blond, light brown, dark brown, or black), childhood reaction to sun (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan [NHS only]), and mole count (0, 1-5, 6-14, or ≥15); model 4, multivariable-adjusted model adjusting for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d), number of sunburns (0, 1-2, 3-5, 6-9, or ≥10), average sun exposure (<1, 2-5, 6-10, or ≥11 h), and ambient ultraviolet flux (in tertiles); and model 5, multivariable-adjusted model adjusting for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d), hair color (red, blond, light brown, dark brown, or black), childhood reaction to sun (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan [NHS only]), mole count (0, 1-5, 6-14, or ≥15), number of sunburns (0, 1-2, 3-5, 6-9, or ≥10), average sun exposure (<1, 2-5, 6-10, or ≥11 h), and ambient ultraviolet flux (in tertiles).
BMI, Body mass index; *CI*, confidence interval; *FHx*, family history of melanoma; *HPFS*, Health Professionals Follow-Up Study; *HR*, hazard ratio; *NHS*, Nurses' Health Study; *NHS2*, Nurses' Health Study 2.

the same as that explained by extrinsic UV-related factors (HR, 1.25 in model 4 vs 1.31 in model 2 [a 4.6% difference]) for SCC. In the combined meta-analysis of 3 groups, after control for all potential confounders (model 5), compared with those without a family history of melanoma, individuals with a family history of melanoma had a 22% increase in risk of lifetime SCC (HR, 1.22; 95% CI, 1.06-1.40). In the meta-analysis, after control for all potential risk factors, the association between family history of melanoma and SCC was statistically significant for SCCs that develop on the extremities only (HR, 1.22; 95% CI, 1.07-1.40) (Table III).

Family history of melanoma and risk of incident BCC

Table V shows the association between a family history of melanoma and the risk of BCC. The proportion explained by intrinsic UV-related factors (HR, 1.29 in model 3 vs 1.34 in model 2 [a 3.7% difference]) in the association between family history of melanoma and risk of BCC was the same as that explained by extrinsic UV-related factors (HR, 1.29 in model 4 vs 1.34 in model 2 [a 3.7% difference]). In the combined meta-analysis of 3 groups, after control for all potential confounders (model 5), compared with those without a family history of melanoma, individuals with a family history of melanoma had a 27% increase in risk of lifetime BCC (HR, 1.27; 95% CI, 1.12-1.44).

DISCUSSION

The present study has provided a detailed evaluation for the association between a family history of melanoma and melanoma as well as KCs in white individuals based on data from 3 large prospective cohorts of men and women. This study uncovered several interesting findings. First, the association between a family history of melanoma and the risk of melanoma was observed predominantly for melanomas that developed on the trunk, but also to a lesser degree for melanomas that developed on the extremities in older women (1.90 [95% CI, 1.39-2.62]). Second, after controlling for multiple potential intrinsic and extrinsic factors, we observed a significant association between a positive family history of

Table III. HRs (95% CIs) for the association between family history of melanoma and risk of incident melanoma and SCC by anatomic site

Cancer type	Person-years	Cases	Age-adjusted HR (95% CI)	Multivariate-adjusted HR* (95% CI)
Melanoma meta-analysis				
Head or neck				
No FHx	4,481,867	214	1.00	1.00
With FHx	324,148	22	1.63 (1.04-2.54)	1.47 (0.94-2.30)
Trunk				
No FHx	4,481,434	629	1.00	1.00
With FHx	324,072	96	2.19 (1.80-2.66)	1.94 (1.59-2.36)
Extremity				
No FHx	4,481,537	560	1.00	1.00
With FHx	324,106	70	2.06 (1.77-2.41)	1.83 (1.57-2.14)
SCC meta-analysis				
Head or neck				
No FHx	4,107,580	1287	1.00	1.00
With FHx	287,657	99	1.25 (1.02-1.54)	1.15 (0.93-1.41)
Trunk				
No FHx	4,108,435	355	1.00	1.00
With FHx	287,713	33	1.29 (1.08-1.54)	1.17 (0.98-1.41)
Extremity				
No FHx	4,107,867	985	1.00	1.00
With FHx	287,660	99	1.34 (1.17-1.54)	1.22 (1.07-1.40)

CI, Confidence interval; *FHx*, family history of melanoma; *HR*, hazard ratio; *SCC*, squamous cell carcinoma.
*Multivariable-adjusted analyses were performed to adjust for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d), hair color (red, blond, light brown, dark brown, or black), childhood reaction to sun (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan [NHS only]), number of sunburns (0, 1-2, 3-5, 6-9, or ≥10), average sun exposures (<1, 2-5, 6-10, or ≥11 h), and ambient UV flux (in tertiles). Trunk includes the shoulder, hip, upper and lower back, abdomen, thigh, and buttock. Extremities include the upper extremity and lower extremity.

melanoma and KCs, with the stronger association seen for BCCs followed by that for SCCs. For SCCs, the association with a family history of melanoma was seen for SCCs of the extremity only. Finally, both intrinsic and extrinsic UV-related factors contribute to the association between family history of melanoma and risk of 3 types of skin cancer.

A positive family history of melanoma increases the personal risk of melanoma by 3-fold to 8-fold.[42] This association between family history of melanoma and melanoma is largely independent of pigmentary traits and mole count.[2] It is likely that genes not directly involved in pigmentary phenotype are involved in this associated risk. Additionally, familial risk of melanoma may be due at least in part to shared sun-protective habits between family members, as one of the most important extrinsic factors, UVR, is a key factor in initiation of DNA damage and development of skin cancer in all skin types.[43] UVR-induced suppression of the immune system also plays a role in development of many skin cancers.[44] One might suppose that having a close family member with melanoma may encourage more strict sun-protective behavior. This has not been extensively studied, but 1 discouraging study found that only one-third of individuals with a family history of melanoma practice sun-protective behavior.[45]

Melanocytes from distinct anatomic sites have long been suspected to hold variable malignant potential.[46] Several studies have found that host risk factors such as family history of melanoma, high mole count, and light hair are predominantly associated with truncal melanomas.[26-30] Truncal melanomas also tend to be associated with younger age of onset and unrelated to molecular signatures of chronic sun exposure.[26,27] Although our study confirmed that truncal melanomas show the strongest and most consistent association with a family history of melanoma across sexes, we also made the interesting observation that upper and lower extremity melanomas also show familial association in women (HR for the NHS, 1.90; 95% CI, 1.39-2.62) These findings are in agreement with the fact that in the general population, melanomas are more commonly found on the trunk in men and on the lower extremities in women,[47] and they suggest a significant environmental component to melanoma development in our cohorts. The extremities and the

Table IV. HRs (95% CIs) for the association between family history of melanoma and risk of incident SCC

Presence/absence of family history	Person-years	Cases	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)	Model 5 HR (95% CI)
NHS							
No FHx	1,656,630	1338	1.00	1.00	1.00	1.00	1.00
With FHx	92,501	122	1.38 (1.14-1.66)	1.36 (1.13-1.64)	1.31 (1.09-1.58)	1.32 (1.09-1.59)	1.28 (1.07-1.55)
NHS2							
No FHx	2,029,329	469	1.00	1.00	1.00	1.00	1.00
With FHx	176,096	59	1.32 (1.00-1.73)	1.28 (0.98-1.68)	1.23 (0.93-1.61)	1.21 (0.92-1.59)	1.18 (0.90-1.55)
HPFS							
No FHx	445,413	868	1.00	1.00	1.00	1.00	1.00
With FHx	18,795	49	1.28 (0.96-1.70)	1.22 (0.91-1.62)	1.12 (0.84-1.50)	1.13 (0.84-1.50)	1.11 (0.83-1.48)
Meta-analysis							
No FHx	4,131,372	2675	1.00	1.00	1.00	1.00	1.00
With FHx	287,392	230	1.34 (1.15-1.55)	1.31 (1.14-1.50)	1.25 (1.09-1.43)	1.25 (1.09-1.43)	1.22 (1.06-1.40)

Model 1, age-adjusted model; model 2, multivariable-adjusted model adjusting for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), and citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d); model 3, multivariable-adjusted model adjusting for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d), hair color (red, blond, light brown, dark brown, or black), childhood reaction to sun (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan [NHS only]), and mole count (0, 1-5, 6-14, or ≥15); model 4, multivariable-adjusted model adjusting for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d), number of sunburns (0, 1-2, 3-5, 6-9, or ≥10), average sun exposure (<1, 2-5, 6-10, or ≥11 h), and ambient UV flux (in tertiles); and model 5, multivariable-adjusted model adjusting for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d), hair color (red, blond, light brown, dark brown, or black), childhood reaction to sun (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan [NHS only]), mole count (0, 1-5, 6-14, or ≥15), number of sunburns (0, 1-2, 3-5, 6-9, or ≥10), average sun exposure (<1, 2-5, 6-10, or ≥11 h, and ambient UV flux (in tertiles).

CI, Confidence interval; *FHx*, family history of melanoma; *HPFS*, Health Professionals Follow-Up Study; *HR*, hazard ratio; *NHS*, Nurses' Health Study; *NHS2*, Nurses' Health Study 2; *SCC*, squamous cell carcinoma.

trunk are both sites that are typically thought to be intermittently sun exposed. The familial increase in malignant potential of melanocytes compounded by certain environmental factors such as clothing style, allowing for more intermittent sun exposure on the extremities, may account for the observation in the female members of our cohort.

The observation of a positive association between family history of melanoma and KCs in our population is likely multifactorial. First, individuals with a family history of melanomas are also at increased risk of several noncutaneous malignancies,[7,48-51] suggesting an increased baseline propensity for development of all malignancies. Second, family members may share environmental factors such as place of residence, time spent outdoors, and sun-protective behavior, and this possibility was likely not completely controlled for in this study despite our attempt. In some of these cases, the "history of melanoma" in the family members may be referring to melanomas resulting from chronic sun exposure such as lentigo maligna melanomas. Previous study has found that individuals with melanomas on chronically sun-exposed sites rather than truncal melanoma have a higher frequency of precursors to KCs and lower mole count.[28] Other studies were in agreement that head and/or neck melanomas and KCs have shared environmental risk factors and tend to occur in the same individuals.[52] Our study points to the fact that many patients who report a positive family history of melanoma may not have true genetic susceptibility and that a report of a positive history may instead point to familial behavioral habits that could be subject to primary prevention.

The unique relationship between familial predisposition to melanoma and SCCs found on the extremities warrants further investigation. A previous study had found that individuals with head/neck melanomas tend to be at higher risk of KCs on all anatomic sites, whereas individuals with truncal melanomas were at increased risk of KCs on the trunk more than on the head/neck,[53] suggesting a strong environmental link (ie, sun exposure pattern) rather than a genetic link between melanoma and KCs. In the present study, we found that family history of melanoma is a risk factor for SCCs on the

Table V. HRs (95% CIs) for the association between family history of melanoma and risk of incident BCC

FHx	Person-years	Cases	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)	Model 5 HR (95% CI)
NHS							
No FHx	1,656,630	15,798	1.00	1.00	1.00	1.00	1.00
With FHx	92,501	1263	1.32 (1.25-1.40)	1.30 (1.23-1.38)	1.27 (1.20-1.35)	1.27 (1.20-1.34)	1.25 (1.18-1.33)
NHS2							
No FHx	2,029,329	7042	1.00	1.00	1.00	1.00	1.00
With FHx	176,096	1084	1.59 (1.49-1.70)	1.56 (1.46-1.66)	1.47 (1.38-1.57)	1.48 (1.39-1.58)	1.43 (1.34-1.52)
HPFS							
No FHx	445,413	5070	1.00	1.00	1.00	1.00	1.00
With FHx	18,795	259	1.19 (1.05-1.35)	1.16 (1.03-1.32)	1.12 (0.99-1.27)	1.12 (0.99-1.27)	1.10 (0.97-1.25)
Meta-analysis							
No FHx	4,131,372	27,910	1.00	1.00	1.00	1.00	1.00
With FHx	287,392	2606	1.37 (1.17-1.60)	1.34 (1.15-1.56)	1.29 (1.12-1.48)	1.29 (1.13-1.49)	1.27 (1.12-1.44)

Model 1, age-adjusted model; model 2, multivariable-adjusted model adjusting for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), and citrus consumption (<2 times/wk, ≥2-≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d); model 3, multivariable-adjusted model adjusting for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d), hair color (red, blond, light brown, dark brown, or black), childhood reaction to sun (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan [NHS only]), and mole count (0, 1-5, 6-14, or ≥15); model 4, multivariable-adjusted model adjusting for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d), number of sunburns (0, 1-2, 3-5, 6-9, or ≥10), average sun exposure (<1, 2-5, 6-10, or ≥11 h), and ambient UV flux (in tertiles); model 5, multivariable-adjusted model adjusting for age (continuous variable), BMI (<25, 25-29.9, or ≥30 kg/m^2), smoking (never-smokers, past smokers, or current smokers), alcohol intake (0, 0-4.9, 5-9.9, or ≥10 g/d), citrus consumption (<2 times/wk, ≥2 to ≤4 times/wk, >4 times/wk to <1 time/d, or ≥1 time/d), hair color (red, blond, light brown, dark brown, or black), childhood reaction to sun (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan [NHS only]), mole count (0, 1-5, 6-14, or ≥15), number of sunburns (0, 1-2, 3-5, 6-9, or ≥10), average sun exposure (<1, 2-5, 6-10, or ≥11 h), and ambient UV flux (in tertiles).
BCC, Basal cell carcinoma; *CI*, confidence interval; *FHx*, family history of melanoma; *HPFS*, Health Professionals Follow-Up Study; *HR*, hazard ratio; *NHS*, Nurses' Health Study; *NHS2*, Nurses' Health Study 2.

extremities only, and not for SCCs on the head and/or neck and trunk. It is worth noting that traditionally chronically sun-exposed sites such as the head and/or neck are not found to be significantly associated with familial predisposition to melanoma in our population. In addition, it is important to note that this anatomic association between extremity SCC as well as extremity melanomas and family history of melanoma is primarily driven by older women (in the NHS) (HR, 1.35, 95% CI, 1.03-1.76), suggesting that perhaps there is some generational and sex-specific lifestyle factor that may be at play. The epidemiology of skin cancer is indeed evolving with human lifestyle and sun-protective behaviors, as is evidenced by the predominance of left-sided skin cancers—both melanomas[54] and KCs[55]—with asymmetric sun exposure from driving. It is possible that the female members of the population may be more vigilant about photoprotection of the face and neck and preferentially tan the extremities, perhaps for reasons of vanity. Additionally, the extremities may be considered a frequently, intermittently sun-exposed site rather than a chronically sun-exposed site such as the head and/or neck or a rarely, intermittently sun-exposed site such as the trunk, pointing to the importance of both sun exposure pattern and absolute cumulative UVR dosage in melanoma and KC development.

This study further uncovered different contributions from intrinsic and extrinsic factors for melanoma and KCs. For melanoma, adjusting for intrinsic UV-related factors resulted in a slightly greater change in magnitude of HRs (model 3) compared with the change caused by further adjusting for extrinsic UV-related factors (model 4). For KCs, the proportion of association explained by intrinsic UV-related factors (model 3) was similar to the proportion of association explained by extrinsic UV-related factors on the HRs (model 4). These findings suggest that for KCs, both intrinsic UV-related factors and sun-behavioral patterns contribute to the increased risks seen in those with a family history of melanoma. The modest association between family history of melanoma and KCs may be due to inclusion of an extensive list of potential risk factors in our multivariate analysis.

One inherent limitation of the current study is self-reported family history. However, other

self-reported measures from these cohorts have been validated, suggesting a high degree of health literacy and accuracy of self-reported outcomes from these groups.[31,32] Shared geography of residence and sun exposure habits between family members could not be fully controlled or measured, despite controlling for varaibles including number of sunburns, average number of hours spent outdoors, and ambient UV flux. Additionally, a potential confounder is that individuals with a family history of melanoma may participate in screening more frequently,[56,57] resulting in detection bias. However, 1 study intended to evaluate methods of increasing the frequency of full skin checks among at-risk individuals found that less than half of the individuals with a family history of melanoma had undergone a skin check at baseline.[58] There is currently no uniform consensus on whether a full skin examination should be part of a routine health checkup.[59-61] Finally, as with all epidemiologic studies, these findings do not imply causality. Despite its limitations, this study also has several strengths. Family history of melanoma reflects both genetic aggregation and similar sun exposure patterns within families. This study attempts to estimate the association more accurately with high-quality data. To our knowledge, it is the first large, prospective cohort study examining the association between family history of melanoma, SCC, and BCC. This is also the first study to simultaneously take into account site-specific SCC and melanoma and family history of melanoma. Additionally, thanks to the high quality of our data and the degree of detail, our study has been able to adjust for previously identified intrinsic and extrinsic risk factors for skin cancers and identify family history of melanoma as an independent risk factor for melanoma, SCC, and BCC.

This study provides new evidence to guide clinical practice for risk stratification of individuals for skin cancer. Patients with a family history of melanoma have a higher risk of melanoma and are also at risk of KCs. Our results indicate that it is important to consider family history of melanoma in a first-degree relative when discussing risk of all skin cancers.

We acknowledge the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School. We would like to thank the participants and staff of the cohort studies for their valuable contributions as well, as the cancer registries of the following states for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming.

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