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History of Keratinocyte Carcinoma and Risk of Melanoma: A Prospective Cohort Study

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Abstract

Background: The association between history of keratinocyte carcinoma (KC, also known as nonmelanoma skin cancer) and risk of developing invasive melanoma has not been assessed comprehensively using prospective data.
Methods: We followed 91 846 women in the Nurses' Health Study (NHS; 1984–2010), 114 918 women in the NHSII (1989–2011), and 48 946 men in the Health Professionals Follow-up Study (1986–2010) for diagnoses of KC and melanoma biennially. Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) of melanoma associated with history of KC, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). All statistical tests were two-sided.
Results: We documented 1949 melanomas, 38 842 BCCs, and 7462 SCCs over 6.4 million person-years of follow-up. After adjustment for other risk factors, a personal history of KC was associated with an increased risk of melanoma (meta-analysis HR = 2.22, 95% CI = 1.73 to 2.85). The association was more apparent among participants with a history of both BCC and SCC (HR = 3.40, 95% CI = 1.60 to 7.19) than among participants with a history of BCC only (HR = 2.20, 95% CI = 1.80 to 2.70) or SCC only (HR = 1.56, 95% CI = 0.98 to 2.46), and there was a strong risk-increasing trend associated with a higher number of reported KCs removed by surgery ($P_{trend} < .001$). In women, KC history was more strongly associated with head/neck melanomas (HR = 4.17, 95% CI = 2.77 to 6.27) than with trunk or limb melanomas (both HRs < 2.50, $P_{heterogeneity} = .04$).
Conclusions: Our results provide novel insights for the relationship between KC history and risk of developing melanoma, which may be important for melanoma prevention.

Melanoma is the most lethal form of skin cancer, and its incidence has been increasing in the western population over the past several decades (1–3). Keratinocyte carcinomas (KCs), including cutaneous basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most commonly diagnosed malignancies in the United States, with 3.5 million cases diagnosed among 2.2 million Americans each year (4). Both melanoma and KCs can be disfiguring, negatively affect quality of life, and cause substantial economic burden (5). Early case-control or registry-based studies have documented a positive association between KC history and melanoma (6–8), whereas prospective evidence for this relationship has been limited by either a small sample size or the inability to examine it in both women and men (9,10). Few studies have taken into account the subtypes of both KC (ie, BCC and SCC) and melanoma (eg, site-specific melanomas) simultaneously. Although BCC and SCC share similar environmental and host risk factors (eg, sun exposure and high sunburn susceptibility), these two types of skin cancer have heterogeneous disease characteristics. Furthermore, existing evidence suggests strong heterogeneity in risk profiles for melanomas occurring at different body sites (11–13), and it is unclear whether these melanomas are equally associated with history of KC. A substantial portion of KC patients are diagnosed with multiple KCs (4), whereas the impact of multiple

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prior-diagnosed KCs on subsequent risk of melanoma has been unknown. Epidemiologic studies in recent years have reported that associations between skin cancer risk and a number of other environmental factors besides sun exposure either may have protective (eg, caffeine) or potentiate (eg, citrus products) effects on the incidence of skin cancer (14–17). However, little is known about whether these potential skin cancer risk factors may modify the relationship between KC history and melanoma. Therefore, a prospective study with detailed risk factor information collected for KC and melanoma and sufficiently long follow-up is needed to more accurately and comprehensively investigate the relationship between KC history and melanoma.

Our previous study has reported an increased risk of cancer including melanoma in association with history of KC in the Nurses' Health Study (NHS; 1984–2008) and Health Professionals Follow-up Study (HPFS; 1986–2008) (18). However, this previous report did not examine the detailed subgroups of KC in association with the risk of developing melanoma and melanoma subtypes, did not investigate the impact of multiple KCs on melanoma risk, and did not investigate the potential modification of the KC-melanoma association by other melanoma risk factors. Therefore, we conducted a further detailed study using data from the NHS (1984–2010) and HPFS (1986–2010) with extended follow-up and an additional cohort of women, the Nurses' Health Study II (1989–2011).

Methods

Study Populations

The NHS was established in 1976 when 121 700 married, registered, female nurses age 30 to 55 years who resided in the United States at the time of enrollment responded to a baseline questionnaire that included questions about their medical history and lifestyle risk factors. The NHSII was established in 1989 when 116 430 registered female nurses age 25 to 42 years were enrolled using a mailed baseline questionnaire that inquired about medical history and lifestyle practices. The HPFS was established in 1986 when 51 529 US male health professionals age 40 to 75 years completed a baseline questionnaire on lifestyle, diet, and newly diagnosed diseases. Biennial questionnaires were used to collect data on environmental and lifestyle factors and disease outcomes in all three cohorts. Participants resided in around 15 states at enrollment and spread to all states in the United States during the follow-up. The institutional review boards of Partners Health Care System and Harvard School of Public Health approved this study. The participants' completion and return of the self-administered questionnaires implied informed consent.

We inquired about history of KC for the first time in 1984 in the NHS, 1989 in the NHSII, and 1986 in the HPFS. Participants who did not return the baseline questionnaires or had a baseline history of melanoma or other nonskin cancers were excluded. Ninety-one thousand, eight hundred forty-six women in the NHS, 114 918 women in the NHSII, and 48 946 men in the HPFS remained in the study.

Assessment of History of Keratinocyte Carcinoma

Participants reported new diagnoses of SCC and BCC biennially starting in 1984 in the NHS, 1989 in the NHSII, and 1986 in the HPFS. Medical and pathological reports were obtained from participants who reported SCC to confirm the diagnosis. Medical records were not obtained for BCC cases. However, previous validation studies reported a high accuracy of self-reported BCC among subsets of cohort participants (96% in women and 84% in men) based on histopathological findings or medical records (19,20). Participants with confirmed SCC or self-reported BCC diagnosed before a given follow-up cycle were defined as having a history of KC at the beginning of that cycle. Participants were asked "How many squamous or basal cell carcinoma lesions have you ever had removed by surgery, cryotherapy or other means? (Exclude melanoma and benign lesions like moles or actinic keratoses)" in 2004 in NHS, 2005 in NHSII, and 2008 in HPFS with the following response categories: never, 1, 2–4, 5–10, or $\geq$11. The highest two categories were combined to maintain statistical power in data analysis.

Assessment of Melanoma Cases

Participants reported new diagnoses of melanoma biennially during the follow-up. Medical and pathological reports were collected from participants who reported melanoma and were reviewed by study physicians to confirm the diagnosis and retrieve information on tumor histology, including tumor location and Breslow thickness. Our primary end point was invasive melanoma, which was further classified into three site-specific categories according to tumor location: head/neck, trunk, and limbs.

Assessment of Covariates

Information on anthropometric and lifestyle factors for chronic diseases, including body height and weight, smoking status, and physical activity was asked and updated in the biennial follow-up questionnaires. Information on dietary factors, including consumption of citrus products, alcohol, and coffee, was repeatedly collected using a validated food frequency questionnaire at least every four years during the follow-up (17). Data on the following phenotypic and sun exposure–related factors were also collected in the follow-up questionnaires: ethnicities; family history of melanoma in first-degree relatives (parents, siblings, or offspring); natural hair color at an early age (age 21 years in NHS, and age 18 years in NHSII/HPFS); number of moles on extremity (arms in NHS/HPFS and legs in NHSII); skin reaction after prolonged sun exposure as a child/adolescent; number of severe or blistering sunburns; average time spent in direct sunlight in summer months since high school; regular use of sunscreen in summer months; and cumulative UV flux since baseline (a measure of long-term UV exposure) (14,17,21).

Statistical Analysis

In the analyses for KC history and its subtypes, participants contributed to follow-up time from the return month of the baseline questionnaire (June 1984 for NHS, June 1989 for NHSII, January 1986 for HPFS) to the month of the first diagnosis of melanoma or other nonskin cancers, month of death, or the end of follow-up (June 2010 for NHS, June 2011 for NHSII, January 2010 for HPFS), whichever came first. In the analysis for self-reported number of KCs, participants contributed to follow-up time from the return month of the questionnaires asking for the number of KCs removed by surgery (June 2004 for NHS, June 2005 for NHSII, January 2008 for HPFS).

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Table 1. Characteristics of person-years according to history of keratinocyte carcinoma in the Nurses' Health Study (1984–2010), Nurses' Health Study II (1989–2011), and Health Professionals Follow-up Study (1986–2010)*

Characteristic	NHS		NHS II		HPFS	
	No (n = 1 065 559)	Yes (n = 60 642)	No (n = 1 286 044)	Yes (n = 38 040)	No (n = 474 681)	Yes (n = 47 154)
Age, mean (SD), y	53.1 (10.0)	61.2 (8.8)	42.9 (8.0)	48.9 (7.1)	60.6 (10.8)	69.0 (9.7)
Body mass index, Mean (SD), kg/m^2	26.3 (5.3)	25.5 (5.0)	26.0 (6.1)	25.1 (5.4)	25.8 (4.3)	25.8 (3.9)
Physical activity level, Mean (SD), metabolic-equivalent h/wk	17.2 (22.4)	19.3 (24.7)	21.7 (29.4)	25.1 (35.9)	33.1 (39.6)	40.5 (41.0)
Current smoking, %	13.9	12.6	10.0	9.4	6.4	4.6
Past smoking, %	41.2	45.2	24.4	27.4	39.1	38.1
Caucasian ancestry, %	97.2	99.6	95.4	99.1	95.2	97.8
Family history of melanoma, %	9.5	12.3	11.6	16.5	3.9	5.7
Red/blonde hair, %	15.0	21.8	19.4	28.5	13.0	16.6
Arm with moles, %	35.7	44.1	50.1	56.2	31.3	35.7
Painful burn/blisters reaction as a child/adolescent, %	14.0	23.3	23.2	35.1	23.5	34.2
Blistering sunburns, Mean (SD)	8.4 (6.9)	11.3 (7.6)	1.9 (2.3)	2.9 (2.9)	12.7 (12.1)	15.7 (12.9)
Annual UV flux (x10^{-4} RB count), Mean (SD)	123.5 (25.6)	127.8 (27.4)	126.0 (25.1)	130.7 (26.5)	130.6 (27.6)	136.5 (28.8)
Average time spent in direct sunlight in summer months since high school, Mean (SD), h/wk	5.4 (2.9)	5.7 (3.0)	4.4 (1.6)	4.5 (1.5)	10.2 (6.0)	10.6 (6.1)
Regular use of sunscreen in summer months, %	24.0	35.3	81.1	88.4	58.6	74.7
Citrus consumption, Mean (SD), serving/d	0.8 (0.6)	0.8 (0.6)	0.5 (0.6)	0.6 (0.5)	0.9 (0.8)	0.9 (0.7)
Caffeine intake, Mean (SD), mg/d	276.1 (198.1)	265.7 (191.2)	229.4 (190.9)	217.0 (169.9)	221.3 (203.7)	207.3 (184.4)
Alcohol intake, Mean (SD), g/d	5.9 (9.7)	7.1 (10.2)	3.5 (6.1)	4.1 (6.1)	11.1 (14.5)	11.6 (13.7)

*All values except age have been standardized to the age distribution of the study population. HPFS = Health Professionals Follow-up Study; NHS = Nurses' Health Study; RB = Robertson-Berger; UV = ultraviolet.

We used Cox proportional hazards models stratified by age and follow-up intervals to estimate the age-adjusted and multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of overall melanoma and site-specific melanomas associated with KC history, which was treated as a time-dependent variable in the models. We verified the assumption of proportionality by modeling the interaction of KC history with follow-up time and found that inclusion of the time-dependent interaction did not statistically significantly improve the model fit for invasive melanoma (P = .25, likelihood ratio test, in the pooled test). KC history was further divided into the following three categories: BCC only, SCC only, and both BCC and SCC. Multivariable analyses were conducted with adjustment for age, follow-up interval, host risk score (quintiles), average time spent in direct sunlight since high school (<2, 2–5, or ≥ 6 hours/week), cumulative UV flux since baseline (quintiles), regular sunscreen use in summer months (yes or no), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, or ≥ 35.0 kg/m^2), smoking status (never, past, current with 1–14, 15–24, or 25 cigarettes/day), physical activity (quintiles), alcohol intake (0, 0.1–9.9, 10–19.9, 20.0–29.9, or ≥ 30.0 g/day), citrus consumption (quintiles), and caffeine intake (quintiles). To avoid overadjustment, a host risk score was created for each participant using cohort-derived hazard ratios associated with each of the six host risk factors of melanoma (ie, ethnicities, family history of melanoma, natural hair color, number of moles on arms, skin reaction after prolonged sun exposure as a child/adolescent, and number of severe or blistering sunburns) (21) and was adjusted in the models as quintiles. A meta-analysis approach was used to combine the risk estimates in different cohorts using a random effect model. Subgroup analyses were performed for several adjusted variables in the presence of appreciable risk difference over subgroups. Heterogeneity for associations between subgroups of KC and risk of melanoma or melanoma subtypes and potential interaction between history of KC and other skin cancer risk factors were examined with the use of the Q statistic (22). We used the t test to compare the difference in Breslow thickness between melanoma cases with and without history of KC. We used SAS software version 9.2 (SAS Institute Inc., Cary, NC) for all statistical analyses. All statistical tests were two-sided, and the statistical significance level was set at a P value of .05.

Results

We documented 1949 invasive melanomas in three cohorts over 6.4 million person-years of follow-up (772 cases/2 795 275 person-years in NHS, 552 cases/2 573 152 person-years in NHSII, 625 cases/1 009 275 person-years in HPFS). In women, 130 melanomas (9.8%) occurred on head/neck, 421 (31.8%) on trunk, and 739 (55.8%) on limbs; in men, 158 melanomas (25.2%) occurred on head/neck, 268 (42.8%) on trunk, and 129 (20.6%) on limbs. During the follow-up, 38 842 participants (28 074 women and 10 768 men) developed BCC, and 7462 participants (5038 women and 2424 men) developed SCC. Participants with a history of KC appeared to be older and were more likely to have host risk factors (eg, family history of melanoma, natural red/blonde hair, and presence of extremity moles) and higher exposure to UV flux and longer average time spent in direct sunlight (Table 1).

After adjustment for other skin cancer risk factors, a personal history of KC was strongly associated with increased melanoma risk in all three cohorts (Table 2, meta-analysis multivariable-adjusted HR = 2.22, 95% CI = 1.73 to 2.85). Analyses stratified by history of BCC and/or SCC suggested a substantially increased risk of melanoma among those who had been diagnosed with both BCC and SCC (meta-analysis HR = 3.40, 95% CI = 1.60 to 7.19), followed by the risk among those with history of BCC only (meta-analysis HR = 2.20, 95% CI = 1.80 to 2.70) and SCC only (meta-analysis HR = 1.56, 95%

Table 2. Risk of melanoma according to history of keratinocyte carcinoma in the Nurses' Health Study (1984–2010), Nurses' Health Study II (1989–2011), and Health Professionals Follow-up Study (1986–2010)

Cohort/History of KC	No. of cases	No. of person-years	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)*	$P_{heterogeneity}$†
NHS (1984–2010)					
No	581	2 606 050	1.00	1.00	
Yes	191	189 225	3.19 (2.69 to 3.78)	2.68 (2.26 to 3.18)	
BCC only	157	170 355	2.97 (2.48 to 3.56)	2.52 (2.09 to 3.02)	
SCC only	6	8386	2.06 (0.92 to 4.60)	1.82 (0.81 to 4.08)	
BCC and SCC	28	10 484	7.36 (5.00 to 10.8)	5.61 (3.80 to 8.28)	.001
NHS II (1989–2011)					
No	507	2 500 468	1.00	1.00	
Yes	45	72 742	2.92 (2.14 to 3.98)	2.15 (1.57 to 2.94)	
BCC only	43	66 133	3.07 (2.24 to 4.22)	2.28 (1.66 to 3.13)	
SCC only	1	4634	0.98 (0.14 to 7.00)	0.70 (0.10 to 5.02)	
BCC and SCC	1	1974	2.40 (0.34 to 17.1)	1.45 (0.20 to 10.4)	.47
HPFS (1986–2010)					
No	490	918 592	1.00	1.00	
Yes	135	90 684	2.26 (1.84 to 2.77)	1.85 (1.51 to 2.28)	
BCC only	109	75 618	2.23 (1.79 to 2.77)	1.84 (1.48 to 2.30)	
SCC only	12	9154	1.92 (1.07 to 3.43)	1.54 (0.86 to 2.75)	
BCC and SCC	14	5912	3.26 (1.88 to 5.64)	2.43 (1.40 to 4.21)	.52
Meta-analysis for women (NHS/NHS II)					
No	1088	5 106 462	1.00	1.00	
Yes	236	261 965	3.13 (2.69 to 3.63)	2.50 (2.04 to 3.06)	
BCC only	200	236 488	2.99 (2.56 to 3.50)	2.45 (2.09 to 2.88)	
SCC only	7	13 019	1.85 (0.88 to 3.89)	1.58 (0.75 to 3.34)	
BCC and SCC	29	12 458	6.47 (3.21 to 13.0)	4.08 (1.33 to 12.6)	.35
Meta-analysis for women and men (NHS/NHS II/HPFS)					
No	1578	6 025 054	1.00	1.00	
Yes	371	352 649	2.76 (2.19 to 3.48)	2.22 (1.73 to 2.85)	
BCC only	309	312 106	2.71 (2.20 to 3.32)	2.20 (1.80 to 2.70)	
SCC only	19	22 173	1.89 (1.20 to 2.99)	1.56 (0.98 to 2.46)	
BCC and SCC	43	18 370	4.65 (2.29 to 9.45)	3.40 (1.60 to 7.19)	.24

*Multivariable analyses were adjusted for age, follow-up interval, host risk score (quintiles), average time spent in direct sunlight since high school (<2, 2–5, or ≥ 6 hours/week), cumulative UV flux since baseline (quintiles), regular sunscreen use in summer months (yes or no), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, or ≥ 35.0 kg/m^2), smoking status (never, past, current with 1–14, 15–24, or 25 cigarettes/day), physical activity (quintiles), alcohol intake (0, 0.1–9.9, 10–19.9, 20.0–29.9, or ≥ 30.0 g/day), citrus consumption (quintiles), and caffeine intake (quintiles). Meta-analyses for different cohorts were performed using the random effect model. CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NHS = Nurses' Health Study.

†Two-sided $P_{heterogeneity}$ values between history of BCC only, history of SCC only, and history of both BCC and SCC were calculated with the use of the Q statistic (22).

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CI = 0.98 to 2.46) ($P_{heterogeneity}$ = .24) (Table 2). Melanoma cases with a personal history of KC appeared to have a thicker tumor compared with cases without the history in the NHS and HPFS, but not in the NHSII (Supplementary Table 1, available online).

There were statistically significantly increasing trends in melanoma risk over the categories of self-reported KCs removed by surgery in all three cohorts, especially in the NHS and NHSII (Table 3). The meta-analysis multivariable-adjusted hazard ratios for melanoma were 1.98 (95% CI = 1.51 to 2.59) for participants with only one KC, 2.23 (95% CI = 1.58 to 3.14) for two to four KCs, and 3.62 (95% CI = 2.46 to 5.32) for five or more KCs (P_{trend} < .001). Analyses for site-specific melanomas suggested that the association with KC history was slightly apparent for melanomas occurring on head/neck, followed by melanomas occurring on limbs and trunk, and the difference was mostly driven by women (Table 4). In women, the multivariable-adjusted hazard ratio for head/neck melanoma (4.17, 95% CI = 2.77 to 6.27) was stronger than that for trunk melanoma (HR = 2.22, 95% CI = 1.47 to 3.37, $P_{heterogeneity}$ = .03) or limb melanoma (HR = 2.40, 95% CI = 1.96 to 2.94, $P_{heterogeneity}$ = .02).

Subgroup analyses showed that the association between KC history and melanoma tended to be more apparent among participants who lived in areas with low annual UV flux at residence (Table 5). The meta-analysis multivariable-adjusted HR was slightly higher among participants with lower annual UV flux (2.61, 95% CI = 1.87 to 3.65) than among participants with higher annual UV flux at residence (1.83, 95% CI = 1.52 to 2.20, $P_{interaction}$ = .07). This association pattern was similar in women and men (data not shown).

Discussion

In the present study, we provided a detailed evaluation for the association between personal history of KC and risk of invasive melanoma based on data from three large cohorts of women and men. After adjustment for other skin cancer risk factors, we found that participants with a history of both BCC and SCC have a more apparently increased risk of melanoma than participants with a history of BCC only or SCC only. There was a strong increasing trend in melanoma risk associated with a higher number of reported KCs removed by surgery. Analyses for site-specific melanomas suggest that head/neck melanomas were more strongly associated with KC history, particularly in women.

Our results on the increased risk of melanoma in association with personal history of KC were consistent with previous

Table 3. Risk of melanoma according to self-reported number of keratinocyte carcinomas ever removed by surgery in the Nurses' Health Study (2004–2010), Nurses' Health Study II (2005–2011), and Health Professionals Follow-up Study (2008–2010)

Cohort/No. of KC	No. of cases	No. of person-years	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)*
NHS (2004–2010)				
No	165	615 819	1.00	1.00
1	41	78 056	1.97 (1.39 to 2.77)	1.78 (1.26 to 2.52)
2–4	31	54 339	2.14 (1.45 to 3.15)	1.79 (1.21 to 2.65)
≥5	20	15 832	4.78 (2.99 to 7.63)	3.65 (2.27 to 5.87)
P_{trend}†			<.001	<.001
NHS II (2005–2011)				
No	144	549 649	1.00	1.00
1	18	26 492	2.58 (1.58 to 4.21)	2.17 (1.33 to 3.56)
2–4	13	13 677	3.63 (2.05 to 6.41)	2.83 (1.59 to 5.03)
≥5	6	3528	6.32 (2.79 to 14.32)	4.31 (1.89 to 9.85)
P_{trend}†			<.001	<.001
HPFS (2008–2010)				
No	12	24 279	1.00	1.00
1	8	4922	3.20 (1.30 to 7.89)	3.01 (1.21 to 7.49)
2–4	10	5007	3.57 (1.52 to 8.39)	3.09 (1.29 to 7.39)
≥5	5	2493	3.38 (1.17 to 9.77)	2.53 (0.85 to 7.50)
P_{trend}†			.002	.01
Meta-analysis for women (NHS/NHS II)				
No	309	1 165 468	1.00	1.00
1	59	104 548	2.15 (1.62 to 2.85)	1.90 (1.43 to 2.52)
2–4	44	68 016	2.67 (1.60 to 4.44)	2.14 (1.38 to 3.31)
≥5	26	19 360	5.12 (3.41 to 7.68)	3.81 (2.52 to 5.75)
P_{trend}†			<.001	<.001
Meta-analysis for women and men (NHS/NHS II/HPFS)				
No	321	1 189 747	1.00	1.00
1	67	109 470	2.23 (1.70 to 2.91)	1.98 (1.51 to 2.59)
2–4	54	73 023	2.76 (1.89 to 4.03)	2.23 (1.58 to 3.14)
≥5	31	21 853	4.85 (3.32 to 7.09)	3.62 (2.46 to 5.32)
P_{trend}†			<.001	<.001

*Multivariable analyses were adjusted for covariate age, follow-up interval, host risk score (quintiles), average time spent in direct sunlight since high school (<2, 2–5, or ≥ 6 hours/week), cumulative UV flux since baseline (quintiles), regular sunscreen use in summer months (yes or no), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, or ≥ 35.0 kg/m^2), smoking status (never, past, current with 1–14, 15–24 or 25 cigarettes/day), physical activity (quintiles), alcohol intake (0, 0.1–9.9, 10–19.9, 20.0–29.9, or ≥ 30.0 g/d), citrus consumption (quintiles), and caffeine intake (quintiles). Meta-analyses for different cohorts were performed using the random effect model. CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NHS = Nurses' Health Study.
†Two-sided P_{trend} values were calculated with self-reported number of keratinocyte carcinomas ever removed by surgery as an ordinal variable in the model.

Table 4. Risk of site-specific melanoma according to history of keratinocyte carcinoma in the Nurses' Health Study (1984–2010), Nurses' Health Study II (1989–2011), and Health Professionals Follow-up Study (1986–2010)

		Head/neck		Trunk		Limbs		
Cohort/history of KC	No. of person-years	No. of cases	Multivariable-adjusted HR (95% CI)*	No. of cases	Multivariable-adjusted HR (95% CI)*	No. of cases	Multivariable-adjusted HR (95% CI)*	$P_{heterogeneity}$†
NHS (1984–2010)								
No	2 606 050	48	1.00	176	1.00	341	1.00	
Yes	189 225	32	4.45 (2.78 to 7.13)	52	2.59 (1.87 to 3.57)	102	2.44 (1.94 to 3.08)	.07
NHS II (1989–2011)								
No	2 500 412	43	1.00	181	1.00	270	1.00	
Yes	72 740	7	3.40 (1.50 to 7.73)	12	1.65 (0.91 to 3.00)	26	2.28 (1.51 to 3.45)	.37
HPFS (1986–2010)								
No	918 592	114	1.00	216	1.00	102	1.00	
Yes	90 684	44	1.95 (1.34 to 2.83)	52	1.95 (1.40 to 2.71)	27	1.58 (1.00 to 2.51)	.73
Meta-analysis for women (NHS/NHS II)								
No	5 106 555	91	1.00	357	1.00	611	1.00	
Yes	261 953	39	4.17 (2.77 to 6.27)	64	2.22 (1.47 to 3.37)	128	2.40 (1.96 to 2.94)	.04
Meta-analysis for women and men (NHS/NHS II/HPFS)								
No	6 027 262	205	1.00	573	1.00	713	1.00	
Yes	352 919	83	3.01 (1.67 to 5.43)	116	2.16 (1.71 to 2.73)	155	2.20 (1.75 to 2.76)	.59

*Multivariable analyses were adjusted for covariate age, follow-up interval, host risk score (quintiles), average time spent in direct sunlight since high school (<2, 2–5, or ≥ 6 hours/week), cumulative UV flux since baseline (quintiles), regular sunscreen use in summer months (yes or no), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, or ≥ 35.0 kg/m^2), smoking status (never, past, current with 1–14, 15–24 or 25 cigarettes/day), physical activity (quintiles), alcohol intake (0, 0.1–9.9, 10–19.9, 20.0–29.9, or ≥ 30.0 g/d), citrus consumption (quintiles), and caffeine intake (quintiles). Meta-analyses for different cohorts were performed using the random effect model. CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NHS = Nurses' Health Study.
†Two-sided $P_{heterogeneity}$ values were calculated with the use of the Q statistic (22).

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Table 5. Risk of melanoma according to history of keratinocyte carcinoma in subgroups in the Nurses' Health Study (1984–2010), Nurses' Health Study II (1989–2011), and Health Professionals Follow-up Study (1986–2010)

Covariate/history of KC	No. of cases	No. of person-years	Multivariable-adjusted HR (95% CI)*	No. of cases	No. of person-years	Multivariable-adjusted HR (95% CI)*	$P_{interaction}$†
Annual UV flux							
		Below median			Above median		
No	867	3 554 871	1.00	707	2 463 036	1.00	
Yes	209	180 875	2.61 (1.87 to 3.65)	162	172 629	1.83 (1.52 to 2.20)	.07
BCC only	181	162 002	2.70 (2.12 to 3.44)	128	150 690	1.74 (1.42 to 2.12)	.006
SCC only	7	8256	1.61 (0.76 to 3.40)	12	11 854	1.68 (0.94 to 3.00)	.90
BCC and SCC	21	8448	3.19 (0.85 to 12.0)	22	8984	3.49 (2.23 to 5.44)	.88
Regular sunscreen use in summer months							
	No			Yes			
No	555	2 466 637	1.00	853	2 708 028	1.00	
Yes	148	148 930	2.45 (2.03 to 2.97)	193	168 160	2.25 (1.50 to 3.38)	.72
BCC only	113	132 123	2.28 (1.63 to 3.17)	167	147 206	2.28 (1.62 to 3.22)	.98
SCC only	7	8191	1.74 (0.82 to 3.72)	12	11 721	1.79 (0.97 to 3.30)	.95
BCC and SCC	28	7653	6.97 (4.66 to 10.5)	14	9234	2.30 (0.72 to 7.33)	.07
Citrus consumption							
		Below median			Above median		
No	673	2 695 163	1.00	817	2 613 924	1.00	
Yes	188	171 027	2.61 (2.01 to 3.38)	178	176 238	1.86 (1.28 to 2.70)	.15
BCC only	155	150 887	2.57 (1.92 to 3.43)	149	155 325	1.87 (1.35 to 2.58)	.15
SCC only	12	11 047	2.31 (1.29 to 4.16)	7	11 350	1.08 (0.51 to 2.28)	.12
BCC and SCC	21	9094	3.96 (2.00 to 7.83)	22	9563	4.11 (2.64 to 6.39)	.93
Caffeine intake							
		Below median			Above median		
No	787	2 632 766	1.00	688	2 591 513	1.00	
Yes	192	187 821	1.94 (1.38 to 2.73)	172	155 755	2.56 (2.11 to 3.10)	.17
BCC only	164	165 103	1.99 (1.48 to 2.67)	138	137 561	2.41 (1.99 to 2.93)	.30
SCC only	7	12 090	0.95 (0.45 to 2.02)	12	7802	2.58 (1.44 to 4.64)	.04
BCC and SCC	21	9655	3.23 (2.00 to 5.23)	22	7972	4.81 (2.32 to 9.97)	.37

*Multivariable analyses were adjusted for covariate age, follow-up interval, host risk score (quintiles), average time spent in direct sunlight since high school (<2, 2–5, or ≥ 6 hours/week), cumulative UV flux since baseline (quintiles), regular sunscreen use in summer months (yes or no), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, or ≥ 35.0 kg/m^2), smoking status (never, past, current with 1–14, 15–24 or 25 cigarettes/day), physical activity (quintiles), alcohol intake (0, 0.1–9.9, 10–19.9, 20.0–29.9, or ≥ 30.0 g/d), citrus consumption (quintiles), and caffeine intake (quintiles). Meta-analyses for different cohorts were performed using the random effect model. BCC = basal cell carcinoma; CI = confidence interval; HR = hazard ratio; SCC = squamous cell carcinoma; UV = ultraviolet.

†Two-sided $P_{interaction}$ values were calculated with the use of the Q statistic comparing the subgroup-specific multivariable-adjusted hazard ratios calculated by meta-analysis (22).

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reports, except that the risk estimate tended to be lower in the present study (multivariable-adjusted HR = 2.22) than those reported in previous case-control or registry-based studies (HR/meta-analysis relative risk > 2.70) (6–8) and in a prospective study with a total of 19 174 individuals and a 16-year follow-up (multivariable-adjusted relative risk = 7.94) (9). The modest associations reported in our study may be partly explained by the adjustment for a number of potential risk factors. In the present study, we were able to investigate the association among both women and men with a larger sample size and further differentiate between BCC and SCC based on detailed cohort follow-up information. We found that participants with a history of both BCC and SCC had a more apparently increased risk of melanoma when compared with participants with a history of BCC or SCC alone, thus adding further evidence to our previous report on the association between KC history and melanoma in the NHS and HPFS (18). However, the statistical test for the heterogeneity between history of BCC or SCC alone and history of both BCC and SCC did not reach statistical significance, and further studies are needed to confirm our findings. We also found that participants who reported a higher number of KCs had a substantially increased risk of melanoma when compared with those who reported no KC removed by surgery. Nevertheless, it is possible that individuals with a prior history of KC or multiple KCs may be more aware of their health conditions and thus seek more frequent medical examinations to allow for early detection of melanoma, resulting in overdiagnosis of melanoma cases among individuals with a history of KC. Our data also partially support the possibility of detection bias, as shown by a slightly lower mean thickness of melanomas among participants with a history of KC in the NHS and HPFS (Table S1). However, melanomas among the NHSII participants with a history of KC had a higher mean thickness than melanomas among those without the history, suggesting potential heterogeneity in the detection bias between older participants (NHS and HPFS) and younger participants (NHSII), which merits further investigation. In addition, there is also a possibility that some of these melanomas would be indolent, or that they would regress naturally, and future studies are needed to clarify these issues.

A strong literature exists for the different risk factor profiles for melanomas occurring at different body sites. Head/neck melanomas have been more closely associated with chronic sun exposure, trunk melanomas have been more closely associated with intermittent sun exposure (eg, severe sunburn) and host risk factors (eg, presence of moles/nevi), and limb melanomas appear to have an intermediate risk factor profile (11–13).

Our findings are consistent with the existing literature, as demonstrated by the more apparent association between history of KC and head/neck melanomas when compared with those between history of KC and trunk and limb melanomas. Chronic UV exposure is the major established environmental risk factor for KC, and thus a history of KC may imply a history of high continuous UV exposure. However, the difference for site-specific melanomas was apparent in women but not in men, which may be associated with the different sun exposure patterns between genders. In women, head/neck receives the highest UV radiation, followed by that received by limbs, and trunk receives the least exposure. This gradient in sun exposure over the body may be less apparent in men and may have diminished the risk difference for melanomas occurring at different body sites.

In the model analysis, we controlled for a set of host, environmental, lifestyle, and dietary factors, most of which have been associated with risk of melanoma or KC in previous epidemiologic studies (14–16,21,23–25). Interestingly, the association was more apparent among participants who lived in areas with lower annual UV flux. High levels of cumulative UV flux have been associated with increased risk of melanoma in previous studies (21,26). It is thus plausible that having a history of KC may represent a more susceptible state and could raise the risk of melanoma more substantially among individuals with lower UV exposure.

Our study has a number of strengths, including its prospective design, large sample size, long-term follow-up, inclusion of both female and male cohorts, a geographically diverse population from all over the United States, accurate case ascertainment on melanoma, and the ability to control for a number of potential skin cancer risk factors based on the detailed cohort follow-up. These strengths are important for a more accurate evaluation of the association between KC history and subsequent risk of melanoma. Our study also has several limitations. First, our study participants mostly comprised well-educated, white health professionals, which may not be a representative sample of the general population. However, restricting the sample to health professionals also reduces the possibility of introducing a confounding effect associated with socioeconomic status. Second, although BCC self-reports have a high accuracy in our study cohorts, we did not validate BCCs using medical records in the study participants because of the vast cases and high costs. Therefore we do not have specific data on body site distribution of BCC and could not evaluate the association between site-specific KC and melanoma risk.

In summary, our study confirmed that a personal history of KC was strongly associated with increased risk of invasive melanoma in both women and men based on data from three cohort studies. Our study provided several novel insights into the existing literature on KC history and melanoma risk, which may have useful health implications for melanoma prevention in clinical practices. For example, individuals who have been diagnosed with KC should be aware of the potentially increased risk of melanoma, and physicians need to pay more attention to these high-risk individuals, especially those who were previously diagnosed with both BCC and SCC or who had multiple KCs. In women, special attention should be paid to head/neck melanomas among those with a history of KC.

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