Research Article

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Long-term Ultraviolet Flux, Other Potential Risk Factors, and Skin Cancer Risk: A Cohort Study

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Abstract

Background: Few prospective studies have examined the relationship between sun exposure, other potential risk factors, and risk of different skin cancers [including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma] simultaneously.

Methods: We evaluated the association between a number of potential risk factors and skin cancer risk in a cohort of 108,916 US women, the Nurses' Health Study II (1989–2009).

Results: During 2.05 million years of follow-up, we identified 6,955, 880, and 779 diagnoses of BCC, SCC, and melanoma, respectively. Compared with participants in the lowest quintile of cumulative ultraviolet flux in adulthood, participants in the highest quintile had multivariable-adjusted relative risks (RR) of 2.35 ($P_{trend} < 0.0001$) for BCC, 2.53 ($P_{trend} = 0.009$) for SCC, and 0.68 ($P_{trend} = 0.38$) for melanoma. In contrast, the RRs were 1.68 (95% CI, 1.55–1.82) for BCC, 1.68 (95% CI, 1.34–2.11) for SCC, and 1.80 (95% CI, 1.42–2.28) for melanoma for participants with $\geq$5 blistering sunburns when compared with participants without sunburn between ages 15 and 20 years. We found significant interactions between family history of melanoma, number of blistering sunburns between ages 15 and 20 years and BCC risk, and between sunburn reaction as a child/adolescent and SCC risk (all $P_{interaction} < 0.05$).

Conclusion: In a cohort of U.S. women, we found that sun exposures in both early life and adulthood were predictive of BCC and SCC risks, whereas melanoma risk was predominantly associated with sun exposure in early life.

Impact: Our results may have potential implications for the prevention of skin cancers. *Cancer Epidemiol Biomarkers Prev; 23(6); 1080–9. ©2014 AACR.*

Introduction

Skin cancer is the most common malignancy in fair-skinned populations in many countries, and its incidence has been increasing during recent decades in the United States (1, 2). An individual's risk of developing skin cancer depends on both constitutional and environmental factors. The constitutional risk factors of skin cancer include family history, red hair color, melanocytic nevi, sun exposure sensitivity, etc. (3, 4), whereas solar UV radiation is a well-established environmental risk factor (5, 6). Three major types of skin cancer, including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma, have been associated with sun exposure in previous studies (7–12).

However, estimates of skin cancer risk attributed to sun exposure vary substantially because of various methods used for sun exposure measurement. Both timing and intensity of exposure are thought to be important, making it difficult to quantitatively determine sun exposure in epidemiologic studies. Most previous studies in this field had been case–control studies using personal recall of sun exposure–related behaviors (e.g., time spent outdoors) as surrogates for sun exposure, which may subject to recall bias. In contrast, residential history is more reliable and less subject to recall bias. Several case–control studies have shown that UV exposure based on residential history was associated with increased melanoma risk (10, 13). However, prospective studies had been restricted to occupation-related sun exposure (14–16). Furthermore, given that the development of skin cancer depends on both sun exposure and constitutional factors, it is possible that sun exposure may interact with host risk profile to alter an individual's skin cancer risk. More recent studies also revealed that lifestyle-related factors, such as artificial tanning bed use (17–19), weight change (20, 21),

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smoking (22, 23), alcohol intake (24, 25), physical activity (26, 27), and rotating nights shifts (28), may also modify risks of different skin cancers. Currently a comprehensive assessment is lacking for the relationships between chronic sun exposure based on residential history, as well as sun exposure in early life, and risk of different types of skin cancer. In addition, data on potential interactions between sun exposure and other potential risk factors on skin cancer risk are also limited.

In this study, we investigated the relationship between a number of potential risk factors, including chronic sun exposure over long durations in adulthood and sun exposure in early life, and risks of BCC, SCC, and melanoma simultaneously using data from the Nurses' Health Study II (NHS II), a large and well-characterized cohort of U.S. women with 20 years of follow-up.

Materials and Methods

Study population

Our study population consisted of participants in the NHS II, which was established in 1989 when 116,430 registered female nurses between ages 25 and 42 years responded to a baseline questionnaire that included questions about their medical histories and health-related risk factors. Participants resided in 14 states at enrollment, which included California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas. Through the follow-up, participants moved dynamically across the United States because of marriage and frequent professional changes, and now they reside in every U.S. state and therefore provide well representativeness for the sun exposure gradients across the United States. Updated information on health condition and risk factors was collected biennially via mailed questionnaires for all participants. A response rate exceeding 90% has been achieved in each follow-up cycle. This study was approved by the Institutional Review Boards of Brigham and Women's Hospital and Harvard School of Public Health. We consider the participants' completion and return of the self-administered questionnaires as informed consent.

Assessment of skin cancer

Participants reported new cases biennially for all 3 types of skin cancer. Permission is obtained from participants to acquire their medical records if SCC or melanoma is reported. The medical records were reviewed by physicians to confirm the diagnoses of SCC or melanoma. Medical records were not obtained for self-reported BCC. However, previous reports have demonstrated high validity of self-reported BCC, with more than 90% confirmed by pathology records (29, 30). Eligible cases consisted of women with incident BCC, SCC, or melanoma diagnosed any time between the baseline and the last follow-up cycle and without baseline history of any cancer.

Assessment of cumulative UV flux and other potential risk factors

UV flux is a composite estimate of UVB amount reaching the earth's surface based on latitude, altitude, and cloud cover (31), and is measured in Robertson–Berger units (32). A monitoring network of UV radiation based on Robertson–Berger meters has been established across the continental United States, and UV flux in Robertson–Berger units used in this study was calculated based on the detailed methodology documented previously (10, 31, 32). A Robertson–Berger meter unit corresponds to approximate 0.068 mJ/cm^2, and 440 units may produce a typical sunburn reaction to untanned Caucasian skin (31). The measured energy is a weighted average of wavelength-specific energy in the range 280 to 330 nm, with weight proportional to the biologic activity of the wavelength (10). Generally, Robertson–Berger data provide information on UVB (280–315 nm) and part of UVA (315–330 nm) received in Robertson–Berger units over 6 month intervals, and a participant was exposed to various UV fluxes as she moved from residence to residence. Cumulative UV flux for a participant that could have received over a period of time was estimated by summing up the 6-month Robertson–Berger unit counts over the follow-up. In this study, participants' residence was known from mailing addresses of the participants throughout the 2-year follow-up cycles since baseline, and we calculated the cumulative UV flux for each participant based on the updated residence information over the follow-up. Place of residence for each participant was rounded off to the biennial June of each odd numbered cycle year because no data are available mid-cycle. If a participant moved during the follow-up cycle, we assumed that she spent the entire cycle (2 years) at the residence that she indicated at the end of the cycle.

Information on a number of other potential risk factors of skin cancer was also collected through the biennial questionnaires. Number of moles on legs, skin reaction after 2 hours of sun exposure as a child/adolescent, and number of blistering sunburns between ages 15 and 20 years were asked on the baseline questionnaire in 1989. Family history of melanoma was first asked on the baseline questionnaire and updated on 1997, 2001, and 2005 questionnaires. Natural hair color at age 20 was asked in 1991. Information on artificial tanning bed use in early life (high school and ages 25–35 years) was collected in 2005. Height was reported in 1989. Information on weight, smoking, rotating night shifts, and menopausal status was updated during each follow-up cycle. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared for each follow-up cycle. Alcohol intake was available in 1991, 1995, 1999, 2003, and 2007, and physical activity was assessed in 1989, 1991, 1997, 2001, and 2005. A directed acyclic graph showing the relationships between sun exposure, other potential risk factors, and risk of skin cancer could be found in Supplementary Fig. S1.

Statistical analysis

The participants were restricted to Caucasian women who had no baseline history of any cancer. Participants who had missing residence information during cohort follow-up were excluded, and those who reported any type of skin cancer or died during follow-up were also excluded from subsequent follow-up. Person-time was calculated for each participant from the date of baseline questionnaire return (1989) to the date of the first report of skin cancer, death, or the end of follow-up (June 2009), whichever came first.

Cox proportional hazards models stratified by follow-up cycles were used to estimate the age-adjusted and multivariable-adjusted relative risks (RRs) with 95% confidence intervals (CI) of skin cancer associated with potential risk factors. Multivariable-adjusted analyses were conducted with adjustment for cumulative UV flux (in quintiles), age, family history of melanoma (yes or no), natural hair color (red, blonde, light brown, dark brown, or black), number of moles on legs (none, 1–2, 3–9, or $\geq$10), sunburn reaction as a child/adolescent (none/some redness, burn, or painful burn/blisters), number of blistering sunburns between ages 15 and 20 years (none, 1–4, or $\geq$5), average tanning bed use in early life (none, 1–2, 3–5, or $\geq$6 times/month), BMI (<24.9, 25–29.9, 30–34.9, and $\geq$35 kg/m^2), alcohol intake (0, <5.0, 5.0–9.9, or $\geq$10.0 g/d), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, or $\geq$27.0 metabolic equivalent hours/week), smoking status (no, past, current smoking with 1–14, 15–24, or $\geq$25 cigarettes/d), rotating night shifts (never, 1–2, 3–9, or $\geq$10 years), and menopausal status (yes or no). Variables were included as dichotomous or categorical variables except age as a continuous variable. For time-varying variables (e.g., cumulative UV flux, smoking status), we used updated information for each 2-year questionnaire cycle during the follow-up. The present cohort included 10 2-year follow-up cycles, and each time the Cox model was run over these follow-up cycles to provide an overall risk estimate for a given risk factor category. Trend tests for cumulative UV flux were carried out using cumulative UV flux as a continuous variable. Multiplicative interactions between cumulative UV flux and other potential risk factors of skin cancer were tested sequentially in multivariable-adjusted models each at a time. Finally, a total host risk score for each participant was calculated using cohort-derived RRs associated with each of 5 host risk factors of skin cancer (family history of melanoma, natural hair color, number of moles on legs, sunburn reaction as a child/adolescent, and number of blistering sunburns between ages 15 and 20 years), and participants were divided into 2 groups with low and high host risk profiles based on the median of the summed risk score. The association of cumulative UV flux with skin cancer risk was reexamined among participants of each risk group.

All statistical analyses were performed using SAS software (version 9.2; SAS Institute Inc.). All statistical tests were 2-tailed, and the significance level was set at $P < 0.05$.

Results

We included 108,916 female Caucasian nurses from the NHS II in the analysis. During 2.05 million person-years of follow-up, we identified 6,955, 880, and 779 diagnoses of BCC, SCC, and melanoma, respectively. Melanoma diagnoses included 445 invasive melanomas and 334 melanomas *in situ*. Table 1 summarizes the baseline age-standardized characteristics of participants by annual UV flux in 1989. Women residing in different areas generally had similar characteristics. Of note, women in the high

Table 1. Age-adjusted characteristics of participants by categories of baseline annual UV flux ($\times 10^4$ Robertson–Berger units) in the Nurses' Health Study II (1989–2009)

	Low ($\leq$110)	Medium (111–124)	High ($\geq$125)
Number of participants	33,999	39,480	35,282
Age (y)[a]	34.0 (4.7)	34.4 (4.7)	34.5 (4.6)
Family history of melanoma, %	12.5	11.5	12.5
Red/blonde hair, %	19.5	19.0	22.5
Number of moles on legs $\geq$10, %	12.9	14.8	15.4
Painful burn/blisters reaction as a child/adolescent, %	24.8	22.9	25.0
Number of blistering sunburns $\geq$5 between ages 15 and 20 years, %	8.9	8.7	12.3
Tanning bed use in early life, %	21.6	27.5	23.9
Body mass index (kg/m^2), mean (SD)	24.1 (5.0)	24.4 (5.2)	23.8 (4.9)
Current smoking, %	15.1	13.5	11.4
Alcohol intake (g/d), mean (SD)	3.3 (6.0)	2.6 (5.5)	3.6 (6.8)
Physical activity (metabolic equivalent h/wk), mean (SD)	25.9 (37.8)	23.6 (34.7)	25.4 (37.3)
Current rotating night shifts, %	60.2	64.3	60.1
Menopause status, %	1.8	2.4	2.8

NOTE: Values are means (SD) or percentages and are standardized to the age distribution of the study population.
[a]Value is not age adjusted.

category tended to have a higher proportion of number of blistering sunburns ≥5 between ages 15 and 20 years.

We found strong exposure–response relationships between cumulative UV flux and risks of BCC and SCC (Table 2). The multivariable-adjusted RRs ranged from 1.34 (95% CI, 1.09–1.66) for the second quintile to 2.35 (95% CI, 1.79–3.07) for the fifth quintile versus the first quintile for BCC ($P_{trend} < 0.0001$), and ranged from 1.37 (95% CI, 0.69–2.74) for the second quintile to 2.53 (95% CI, 1.11–5.77) for the fifth quintile versus the first quintile for SCC ($P_{trend} = 0.009$). However, there was no association between cumulative UV flux and risk of melanoma.

We included a number of potential risk factors of skin cancer in this analysis, and most of them showed appreciable associations with skin cancer risk (Table 3). Number of blistering sunburns between ages 15 and 20 years, which could serve as an indicator for sun exposure in early life, showed strong associations with all 3 types of skin cancer. The RRs were 1.68 (95% CI, 1.55–1.82) for BCC, 1.68 (95% CI, 1.34–2.11) for SCC, and 1.80 (95% CI, 1.42–2.28) for melanoma for participants with 5 or more blistering sunburns when compared with participants without sunburn. Participants with red hair color and higher sunburn reaction susceptibility as a child/adolescent were also more likely to develop a skin cancer of any type. Family history of melanoma and number of moles on legs were most strongly associated with melanoma risk, followed by BCC risk. Higher BMI was associated with decreased risks of BCC and SCC, whereas higher alcohol intake was associated with increased risks of BCC and melanoma. Interestingly, participants with higher physical activity levels were at a higher risk to develop BCC, whereas participants with longer duration of rotating night shifts were at a lower risk to develop BCC. Menopausal status also showed a marginal association with BCC risk. We also conducted separate analyses for invasive melanoma and melanoma *in situ*, and results suggest generally similar associations as reported for overall melanoma (data available upon request). For example, the RRs were 1.80 (95% CI, 1.31–2.48) for invasive melanoma and 1.78 (95% CI, 1.25–2.55) for melanoma *in situ* for participants with 5 or more blistering sunburns when compared with participants without sunburn between ages 15 and 20 years.

We found that there were significant interactions between cumulative UV flux and family history of

Table 2. Relative risks of skin cancer according to quintiles[a] of cumulative UV flux in the Nurses' Health Study II (1989–2009)

	Cases	Age-adjusted RR (95% CI)	MV-adjusted RR[b] (95% CI)
BCC			
Quintile 1	664	1.00	1.00
Quintile 2	829	1.40 (1.13–1.74)	1.34 (1.09–1.66)
Quintile 3	1,082	1.75 (1.37–2.24)	1.63 (1.27–2.08)
Quintile 4	2,023	2.09 (1.60–2.72)	1.91 (1.46–2.48)
Quintile 5	2,357	2.64 (2.01–3.46)	2.35 (1.79–3.07)
P_{trend}		<0.0001	<0.0001
SCC			
Quintile 1	45	1.00	1.00
Quintile 2	91	1.39 (0.70–2.78)	1.37 (0.69–2.74)
Quintile 3	156	1.75 (0.80–3.82)	1.71 (0.79–3.73)
Quintile 4	277	2.21 (0.98–4.99)	2.16 (0.96–4.85)
Quintile 5	311	2.62 (1.15–5.99)	2.53 (1.11–5.77)
P_{trend}		0.003	0.009
Melanoma			
Quintile 1	97	1.00	1.00
Quintile 2	159	0.75 (0.44–1.28)	0.74 (0.44–1.25)
Quintile 3	149	0.64 (0.35–1.17)	0.60 (0.33–1.09)
Quintile 4	218	0.81 (0.42–1.56)	0.72 (0.37–1.38)
Quintile 5	156	0.79 (0.40–1.58)	0.68 (0.34–1.34)
P_{trend}		0.98	0.38

[a]Cumulative UV flux quintiles: Quintile 1 = 186–616, Quintile 2 = 617–1,078, Quintile 3 = 1,079–1,581, Quintile 4 = 1,582–2,034, and Quintile 5 = 2,035–3,920 × 10^4 Robertson–Berger units, respectively.

[b]MV-adjusted RR: multivariable analysis controlled for age, family history of melanoma, natural hair color, number of moles on legs, sunburn reaction as a child/adolescent, number of blistering sunburns between ages 15 and 20 years, average tanning bed use in early life, body mass index, alcohol intake, physical activity, smoking status, rotating night shifts, and menopausal status.

Table 3. Interactions between cumulative UV flux and potential risk factors of skin cancer in the Nurses' Health Study II (1989–2009)

	BCC				SCC				Melanoma			
	Cases	Person-years (thousands)	MV-adjusted RR[a] (95% CI)	*P* for interaction[b]	Cases	Person-years (thousands)	MV-adjusted RR[a] (95% CI)	*P* for interaction[b]	Cases	Person-years (thousands)	MV-adjusted RR[a] (95% CI)	*P* for interaction[b]
Family history of melanoma												
No	5778	1805	1.00		747	1788	1.00		604	1804	1.00	
Yes	1177	247	1.37 (1.28–1.46)	**0.006**	133	243	1.17 (0.97–1.41)	0.947	175	246	1.80 (1.52–2.13)	0.561
Natural hair color												
Red	432	68	1.51 (1.36–1.67)		62	66	1.56 (1.18–2.05)		59	68	1.97 (1.48–2.63)	
Blonde	1243	290	1.13 (1.06–1.21)		155	286	1.09 (0.90–1.32)		164	290	1.27 (1.05–1.54)	
Light brown	2491	704	1.00		330	696	1.00		289	703	1.00	
Dark brown	2016	693	0.89 (0.84–0.94)		269	687	0.90 (0.76–1.06)		202	692	0.77 (0.65–0.93)	
Black	79	30	0.92 (0.74–1.15)	0.054	3	30	0.27 (0.09–0.84)	0.299	3	30	0.32 (0.10–1.01)	0.162
Number of moles on legs												
None	2970	986	1.00		429	978	1.00		243	987	1.00	
1–2	1279	376	1.10 (1.03–1.17)		152	372	0.90 (0.75–1.09)		123	376	1.29 (1.04–1.60)	
3–9	1187	335	1.13 (1.06–1.21)		134	332	0.87 (0.72–1.06)		154	335	1.81 (1.47–2.21)	
≥10	1244	282	1.35 (1.26–1.44)	0.419	132	279	0.99 (0.81–1.20)	0.970	232	281	3.04 (2.54–3.65)	0.555
Sunburn reaction as a child/adolescent												
None/some redness	2756	1070	1.00		334	1062	1.00		316	1069	1.00	
Burn	1894	490	1.37 (1.29–1.45)		221	484	1.36 (1.14–1.62)		212	489	1.24 (1.04–1.48)	
Painful burn/blisters	2291	488	1.60 (1.50–1.70)	0.276	325	481	1.93 (1.63–2.28)	**0.033**	251	488	1.36 (1.14–1.63)	0.385
Number of blistering sunburns between ages 15–20												
None	1690	686	1.00		213	682	1.00		181	685	1.00	
1–4	4172	1160	1.30 (1.23–1.38)		517	1148	1.25 (1.06–1.47)		463	1160	1.32 (1.11–1.57)	
≥5	1075	198	1.68 (1.55–1.82)	**<0.001**	143	194	1.68 (1.34–2.11)	0.745	131	198	1.80 (1.42–2.28)	0.210
Average tanning bed use in early life (high school and ages 25–35)												
None	4005	1098	1.00		549	1086	1.00		494	1098	1.00	
1–2 times/mo	843	208	1.19 (1.10–1.28)		130	205	1.48 (1.22–1.79)		94	208	1.01 (0.81–1.27)	
3–5 times/mo	262	67	1.20 (1.06–1.37)		43	66	1.65 (1.21–2.26)		37	67	1.27 (0.90–1.77)	
≥6 times/mo	382	80	1.59 (1.43–1.77)	0.609	50	79	1.78 (1.33–2.39)	0.759	41	79	1.24 (0.89–1.71)	0.094
Body mass index, kg/m^2												
<24.9	3954	1103	1.00		511	1091	1.00		459	1103	1.00	
25–29.9	1748	511	0.81 (0.77–0.86)		238	507	0.79 (0.68–0.92)		180	511	0.81 (0.68–0.96)	
30–34.9	737	244	0.69 (0.64–0.75)		81	242	0.53 (0.42–0.68)		73	244	0.70 (0.54–0.90)	
≥35	499	188	0.60 (0.54–0.66)	0.358	49	186	0.41 (0.30–0.55)	0.621	66	188	0.83 (0.63–1.09)	0.322
Smoking status												
No	4379	1317	1.00		508	1305	1.00		511	1316	1.00	
Past	1954	492	1.06 (1.00–1.12)		276	486	1.20 (1.04–1.40)		211	492	0.99 (0.84–1.17)	

(Continued on the following page)

Table 3. Interactions between cumulative UV flux and potential risk factors of skin cancer in the Nurses' Health Study II (1989–2009) (Cont'd)

	BCC				SCC				Melanoma			
	Cases	Person-years (thousands)	MV-adjusted RR[a] (95% CI)	*P* for interaction[b]	Cases	Person-years (thousands)	MV-adjusted RR[a] (95% CI)	*P* for interaction[b]	Cases	Person-years (thousands)	MV-adjusted RR[a] (95% CI)	*P* for interaction[b]
Current 1–14 cigs/d	286	94	0.96 (0.85–1.08)		52	93	1.48 (1.11–1.97)		25	94	0.69 (0.46–1.03)	
Current 15–24 cigs/d	205	75	0.93 (0.80–1.07)		30	75	1.18 (0.81–1.70)		22	75	0.82 (0.54–1.27)	
Current ≥25 cigs/d	78	31	0.88 (0.71–1.11)	0.187	9	30	0.89 (0.46–1.73)	0.604	7	31	0.67 (0.32–1.42)	0.363
Alcohol intake, g/d												
0	1808	611	1.00		231	605	1.00		211	611	1.00	
<5.0	1958	560	1.14 (1.07–1.22)		268	553	1.18 (0.99–1.41)		236	559	1.18 (0.98–1.42)	
5.0–9.9	711	172	1.15 (1.06–1.26)		96	170	1.11 (0.87–1.41)		81	172	1.20 (0.93–1.56)	
≥10	1040	191	1.31 (1.21–1.41)	0.105	148	188	1.23 (0.99–1.53)	0.777	116	191	1.47 (1.16–1.86)	0.058
Physical activity, metabolic equivalent hours/week												
<3.0	895	289	1.00		123	286	1.00		111	289	1.00	
3.0–8.9	1206	387	1.05 (0.96–1.15)		163	382	1.06 (0.84–1.34)		142	386	0.94 (0.74–1.21)	
9.0–17.9	1263	363	1.10 (1.01–1.20)		166	359	1.08 (0.85–1.36)		134	363	0.93 (0.72–1.19)	
18.0–26.9	854	225	1.15 (1.05–1.27)		113	223	1.12 (0.86–1.45)		102	225	1.11 (0.84–1.45)	
≥27.0	1821	428	1.23 (1.14–1.34)	0.687	243	423	1.24 (0.99–1.55)	0.603	219	427	1.25 (0.99–1.58)	0.072
Rotating night shifts												
Never	1506	434	1.00		199	429	1.00		176	433	1.00	
1–2 years	1342	387	0.97 (0.90–1.05)		183	382	1.00 (0.82–1.23)		168	387	1.03 (0.83–1.27)	
3–9 years	1438	440	0.91 (0.85–0.98)		188	435	0.91 (0.75–1.12)		206	440	1.11 (0.90–1.36)	
≥10 years	291	85	0.85 (0.75–0.96)	0.372	45	84	0.94 (0.68–1.31)	0.976	37	85	0.98 (0.69–1.41)	0.279
Menopausal status												
Premenopause	4054	1409	1.00		445	1393	1.00		538	1407	1.00	
Postmenopause	2073	351	0.92 (0.85–0.99)	0.688	325	348	1.05 (0.86–1.28)	0.641	172	352	1.01 (0.80–1.27)	0.233

NOTE: Bold indicates $P < 0.05$.

[a]Based on multivariable analysis controlled for covariates listed in Table 2 (footnote b).

[b]We tested the significance of the interaction with a likelihood ratio test by comparing a model with the main effects of cumulative UV flux and the stratifying variable and their interaction terms with a reduced model with only the main effects.

Table 4. Relative risks of skin cancer according to quintiles of cumulative UV flux stratified by host risk score in the Nurses' Health Study II (1989–2009)

	Low host risk score[a]			High host risk score[a]			
	Cases	Age-adjusted RR (95% CI)	MV-adjusted RR[b] (95% CI)	Cases	Age-adjusted RR (95% CI)	MV-adjusted RR[b] (95% CI)	*P*-value for interaction[c]
BCC							
Quintile 1	224	1.00	1.00	440	1.00	1.00	0.758
Quintile 2	281	1.45 (0.99–2.11)	1.43 (0.98–2.08)	548	1.33 (1.02–1.72)	1.30 (1.00–1.68)	
Quintile 3	413	2.01 (1.30–3.10)	1.97 (1.28–3.04)	669	1.52 (1.12–2.05)	1.47 (1.09–1.98)	
Quintile 4	697	1.90 (1.19–3.03)	1.87 (1.18–2.98)	1326	2.00 (1.45–2.76)	1.93 (1.40–2.66)	
Quintile 5	817	2.51 (1.56–4.03)	2.45 (1.53–3.94)	1540	2.41 (1.74–3.35)	2.30 (1.66–3.19)	
P_{trend}		<0.0001	<0.0001		<0.0001	<0.0001	
SCC							
Quintile 1	15	1.00	1.00	30	1.00	1.00	0.205
Quintile 2	30	1.14 (0.35–3.73)	1.15 (0.36–3.71)	61	1.49 (0.63–3.51)	1.48 (0.63–3.49)	
Quintile 3	50	2.08 (0.56–7.77)	2.15 (0.58–7.95)	106	1.48 (0.56–3.89)	1.47 (0.56–3.87)	
Quintile 4	97	3.14 (0.78–12.6)	3.29 (0.83–13.0)	180	1.70 (0.62–4.65)	1.69 (0.62–4.63)	
Quintile 5	118	4.03 (0.98–16.5)	4.27 (1.05–17.3)	193	1.89 (0.68–5.25)	1.88 (0.68–5.23)	
P_{trend}		0.01	0.008		0.16	0.17	
Melanoma							
Quintile 1	29	1.00	1.00	68	1.00	1.00	0.423
Quintile 2	31	0.44 (0.15–1.28)	0.45 (0.16–1.30)	128	0.87 (0.48–1.59)	0.87 (0.48–1.58)	
Quintile 3	47	0.50 (0.15–1.70)	0.51 (0.15–1.71)	102	0.64 (0.32–1.29)	0.63 (0.32–1.25)	
Quintile 4	67	0.53 (0.14–1.95)	0.53 (0.14–1.94)	151	0.84 (0.39–1.79)	0.81 (0.38–1.72)	
Quintile 5	40	0.47 (0.12–1.80)	0.46 (0.12–1.76)	116	0.83 (0.38–1.84)	0.80 (0.36–1.75)	
P_{trend}		0.51	0.44		0.90	0.71	

[a]We used the lowest quintile with each subgroup as the reference.

[b]MV-adjusted RR: multivariable analysis controlled for covariates listed in Table 2 (footnote b).

[c]We tested the significance of the interaction with a likelihood ratio test by comparing a model with the main effects of cumulative UV flux and host risk profile and their interaction terms with a reduced model with only the main effects.

melanoma ($P_{interaction} = 0.006$) and number of blistering sunburns between ages 15 and 20 years ($P_{interaction} < 0.001$) on BCC risk, and between cumulative UV flux and sunburn reaction as a child/adolescent ($P_{interaction} = 0.033$) on SCC risk (Table 3). Stratified analyses suggested heterogeneous associations between cumulative UV flux and risks of BCC and SCC in different variable categories (Supplementary Tables S1 and S2). Analyses using the lowest quintile of the subgroup with the lowest perceived skin cancer risk (e.g., participants with no family history of melanoma or no blistering sunburns) as the reference yielded substantially higher RRs for subgroups with higher perceived skin cancer risk (e.g., participants with family history of melanoma or number of blistering sunburns $\geq$5) when compared with analyses using the lowest quintile within each subgroup as the reference. For example, the multivariate-adjusted RR for SCC was 1.96 (95% CI, 0.50–7.71) for the fifth quintile versus the first quintile among participants with "painful burn/blisters" reaction as a child/adolescent, and it was elevated to 4.22 (95% CI, 1.69–10.5) when compared to the first quintile of participants with "none/some redness" reaction as a child/adolescent (Supplementary Table S2). Although no significant interactions were found between cumulative UV flux and potential risk factors on melanoma risk, 3 variables, including alcohol intake, physical activity, and tanning bed use, showed interactions of marginal significance ($P_{interaction} < 0.10$) with cumulative UV flux.

Although there was no significant interaction between cumulative UV flux and host risk score, we found heterogeneous associations between cumulative UV flux and SCC risk among participants with low and high host risk profiles (Table 4). The multivariable-adjusted RRs of SCC for the highest quintile versus the lowest quintile of cumulative UV flux were 4.27 (95% CI, 1.05–17.3) for participants with low host risk score ($P_{trend} = 0.008$), and 1.88 (95% CI: 0.68–5.23) for participants with high host risk score ($P_{trend} = 0.17$) within each subgroup. For BCC and melanoma, the associations with cumulative UV flux were similar in low and high host risk groups. Analyses using the lowest quintile of the low host risk group as the reference suggest increasing trends for risks of all 3 types of skin cancer over the quintiles of low to high host risk groups in age-adjusted models and multivariable models

adjusting for lifestyle-related factors (Supplementary Table S3). However, risk estimates were dramatically lowered after additionally adjusting for host risk factors.

Discussion

In this study, we examined the association of skin cancer risk with a number of potential risk factors, including sun exposures in adulthood and early life, in a prospective cohort study (NHS II) with 20 years of follow-up in the United States. We found consistent increased risks of BCC and SCC in association with cumulative UV flux with adjustment for a number of potential risk factors, whereas melanoma risk did not change materially across the gradients of cumulative UV flux. In contrast, melanoma risk was strongly associated with number of blistering sunburns between ages 15 and 20 years, an indicator of early life sun exposure. Other host risk factors and lifestyle-related factors also showed appreciable associations with different types of skin cancer, and host risk profiles may interact with sun exposure to alter risks of BCC and SCC.

Our findings that chronic sun exposure in adulthood as assessed by cumulative UV flux over long durations were associated with substantially increased risks of BCC and SCC are consistent with the existing literature. An additional novel finding is that cumulative UV flux over long durations may interact with host factors to alter an individual's risk to develop BCC or SCC. For example, when using the lowest quintile within each subgroup as the reference, the magnitude of associations between cumulative UV flux and SCC risk was strikingly higher among participants with none/some redness reaction when compared with those among participants with burn or painful burn/blisters reactions after 2 hours of sun exposure as a child/adolescent (Supplementary Table S2). Blistering sunburn is believed to result from high doses of intense UV radiation exposure in short increments of time and is therefore considered as a measure of intermittent exposure, whereas it is also a measure of host cutaneous sensitivity to sun exposure (12). These results suggest that risk of SCC among participants with lower host risk was more likely to be sun exposure dependent when compared with participants with higher host risk. Analyses stratified by host risk score provided further evidence for the stronger associations between cumulative UV flux and risks of BCC and SCC among participants with low host risk profile, and the difference in magnitude of the associations varied most differentially for SCC among participants with different host risk profiles (Table 4). It has been demonstrated that genetic profile may play roles in host susceptibility to develop skin cancer (33, 34). However, mechanisms underlying the different responses to chronic sun exposure among persons with different risk profiles have been largely unknown, and further studies are needed to clarify these issues.

Our findings do not support the association between cumulative UV flux in adulthood and melanoma risk. However, melanoma risk seemed to be predominantly associated with sun exposure in early life, as evidenced by the strong RRs according to number of blistering sunburns between ages 15 and 20 years (Table 3). Although sun exposure has been regarded as the major environmental risk factor that is responsible for melanoma risk, melanoma may have a more complicated relationship with sun exposure than SCC and BCC (5, 35). Inconsistent results on the association of sun exposure with melanoma risk have been reported. For example, an early study in a cohort of US Navy personnel found have a higher age-adjusted incidence rate of melanoma in persons in indoor occupations than in persons who worked outdoors (10.6/100,000 vs. 9.4/100,000; ref. 36). Another case–control study also found that chronic sun exposure, as indicated by days of outdoor activity during adolescence and by occupation in recent adult life, was significantly associated with reduced melanoma risk in a Canadian population (37). In a more recent meta-analysis, after an extensive analysis of the inconsistencies and variability in the estimates reported in previous observational studies, the authors hypothesized that melanoma risk may show a positive association with intermittent sun exposure and an inverse association with a high continuous pattern of sun exposure (5). Our results also suggest similarly reduced but insignificant RRs of melanoma associated with cumulative UV flux. In contrast, we found that melanoma risk depended heavily on sun exposure in early life and several host risk factors (Table 3). Although the association of melanoma risk with sun exposure in early life has been documented in previous studies (38–40), few prospective studies have compared sun exposures in both adulthood and early life and examined their interaction. In addition, genetic variants associated with host factors have been shown to play important roles in the etiology of melanoma (34, 40, 41), suggesting a complicated mechanism of melanoma development in the context of gene–environment interaction.

Our study has several strengths. First, we were able to assess skin cancer risk associated with a number of potential risk factors, including sun exposures in adulthood and early life, host risk factors, and lifestyle-related factors, over a span of 20 years in a large cohort. Most data were collected before the onset of skin cancer and thus precluded potential recall bias in retrospective studies, which collected exposure information after the onset of disease. Specifically, detailed data on host risk factors allowed us to separate the study population into subgroups with different host risk profiles and helped us identify 2 distinct patterns of the relationship between sun exposure and SCC risk. Second, the cumulative UV flux has several advantages. It captured the addresses changes (residential history) of the participants over the follow-up and was time-dependent, which allowed for assessment of long-term sun exposure. Furthermore, it also accounted for intensity of ambient UV radiation in different areas over the United States. Therefore, it may serve as a better estimation for sun exposure over long durations when compared with subjective measures (e.g., time spent

outdoors, geographic region of residence) used in previous studies. Specifically, UV flux is expected to be better than geographic region of residence as a proxy for sun exposure because it takes into account altitude and cloud cover in addition to latitude. Third, in contrast to most previous studies, which had been restricted to 1 or 2 types of skin cancer, we were able to evaluate the risks of all 3 major types of skin cancer (BCC, SCC, and melanoma) simultaneously in association with cumulative UV flux in the same population. Finally, our cohort has a high response rate exceeding 90% in each follow-up cycle, and our participants were all health professionals who were more likely to provide high-quality data on both exposure and health conditions.

Our study also has its limitations. First, although UV flux may serve as a better measure of sun exposure when compared with subjective measures used in previous studies, it is an approximate estimate of the amount of UV radiation that could have received over a period of time. Long-term UV radiation measured by Robertson–Berger meters may subject to measurement error (42, 43), although there is also supportive evidence for the stability of Robertson–Berger meters over time (44–46). Factors associated with accuracy of the Robertson–Berger meters may include changes in ozone, cloudiness, aerosol concentrations, calibration of sensors, temperature etc. In addition, some personal factors such as use of sunscreen and time spent outdoors may affect the actual quantity of UV radiation received. The estimates of UV doses may be more accurate if personal behaviors related to sun exposure could be incorporated in the estimation (47). To partly control for behavioral heterogeneity among participants, we adjusted for physical activity level and rotating night shifts in the multivariable analyses. Results showed that there were no significant interactions between cumulative UV flux and these variables. Second, BCC cases were not independently validated as SCC and melanoma. However, we previously demonstrated high validity of the BCC self-reports, with more than 90% confirmed by pathology records (29, 30). In addition, our previous studies using self-reported BCC cases identified both constitutional and sun exposure risk factors as expected, such as lighter pigmentation, less childhood and adolescent tanning tendency, and higher tendency to sunburn (11, 48). These data suggest that the bias because of BCC self-reports is likely to be minimal in this study. Third, although we considered a number of risk factors, which may potentially confound the exposure effects of interest, residual confounding by unmeasured variables cannot be ruled out. Fourth, our participants consisted entirely of white women, and thus the generalizability of the results to men and other ethnicities may be limited.

In sum, we found that risks of BCC and SCC were associated with sun exposures in both adulthood and early life, whereas melanoma risk was predominantly associated sun exposure in early life in a cohort of U.S. women. Host factors, including red hair, sun reaction as a child/adolescent, and number of blistering sunburns between ages 15 and 20 years were strong predictors of all 3 types of skin cancer. Several host risk factors may interact with sun exposure to alter risks of BCC and SCC. These findings support heterogeneous associations between sun exposure, other potential risk factors, and risks of different types of skin cancer, and thus may have potential implications for the prevention of skin cancers.

Disclosure of Potential Conflicts of Interest

A.A. Qureshi is a consultant/advisory board member of AbbVie, Amgen, CDC, Janssen, Merck, Novartis, and Pfizer. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: S. Wu, J. Han, A.A. Qureshi
Development of methodology: S. Wu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Han, F. Laden, A.A. Qureshi
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Wu, J. Han, A.A. Qureshi
Writing, review, and/or revision of the manuscript: S. Wu, J. Han, F. Laden, A.A. Qureshi
Study supervision: S. Wu

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