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Original Contribution

History of Severe Sunburn and Risk of Skin Cancer Among Women and Men in 2 Prospective Cohort Studies

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Few studies have assessed the relationship between sunburn and risk of different skin cancers (melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC)) in prospective studies simultaneously, and little is known about the association of severe sunburns at different body sites with skin cancer risk. We used data on 87,166 women in the Nurses' Health Study (1982–2010) and 32,959 men in the Health Professionals Follow-up Study (1992–2010) to investigate skin cancer risk associated with history of severe sunburns at different body sites (face/arms, trunk, and lower limbs). After adjustment for other risk factors, overall baseline history of severe sunburn was more apparently associated with risk of melanoma than with risk of SCC and BCC in men (multivariable-adjusted hazard ratios were 2.41 (95% confidence interval (CI): 1.32, 4.41) for melanoma, 1.48 (95% CI: 1.08, 2.03) for SCC, and 1.18 (95% CI: 1.06, 1.32) for BCC) but not in women. Sunburn on the trunk appeared to be more closely associated with melanoma risk, but not risk of SCC and BCC, when compared with sunburns at other body sites (face/arms and lower limbs). These differences were more apparent in men than in women. Pending further investigation, our findings add novel insights to the existing literature on sunburn history and skin cancer risk.

cohort studies; melanoma; skin cancer; sun exposure; sunburn

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; HPFS, Health Professionals Follow-up Study; KC, keratinocyte carcinoma; NHS, Nurses' Health Study; SCC, squamous cell carcinoma.

Malignant melanoma is a potentially lethal form of skin cancer, and its incidence has been increasing in the United States and worldwide over the past a few decades (1–3). On the other hand, keratinocyte carcinomas (KCs), including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin, are the most commonly diagnosed malignancies in the United States, with 3.5 million cases being diagnosed among 2.2 million Americans each year (4). Both melanoma and KC can be disfiguring, negatively affect quality of life, and cause substantial economic burden (5). Knowledge on risk factors for skin cancer is important for disease prevention and clinical management.

Solar ultraviolet radiation has been recognized as the major environment risk factor for both melanoma and KC. However, existing evidence suggests that different types of skin cancer are associated with different patterns of sun exposure. While risks of SCC and BCC are more closely linked to a continuous, chronic sun exposure pattern (6, 7), risk of melanoma is more strongly associated with a pattern of intermittent sun exposure (8).

Sunburn is an inflammatory reaction that occurs after acute intermittent exposure of the skin to intense solar radiation, and it has been identified as a strong predictor of melanoma risk (8–12). Sunburn has also been associated with increased risks of SCC and BCC (13–15). However, few studies have investigated the associations of sunburn with risk of 3 major skin cancers (melanoma, SCC, and BCC) in the same population. Sunburn has commonly been treated as a general measure of intermittent sun exposure in previous studies, and little is known about the potential influence of anatomical site of the sunburn on risk of skin cancer.

Most previous studies on sunburn history and skin cancer risk have been case-control studies, which may be subject to

information bias because skin cancer patients may overreport or underreport their sunburn experience, producing biased estimates of the true association (7, 16). In addition to established skin cancer risk factors such as host pigmentation traits (e.g., presence of moles, hair color, skin reaction to sun exposure), lifestyle and dietary factors (e.g., physical activity, alcohol and caffeinated coffee intakes) have been associated with altered risk of melanoma and KC in recent years (17–21). Therefore, a prospective study with detailed sunburn history information collected before the occurrence of melanoma and KC and sufficient control for other potential risk factors is necessary to more ideally investigate the value of sunburn history in predicting risk of developing skin cancers.

To address the above questions of interest, we conducted a prospective study using data from 2 large cohort studies of women and men: the Nurses' Health Study (NHS; 1982–2010) and the Health Professionals Follow-up Study (HPFS; 1992–2010).

METHODS

Study populations

The NHS was established in 1976 when 121,700 married, registered, female nurses aged 30–55 years and residing 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 (22). The HPFS was established in 1986 when 51,529 US male health professionals aged 40–75 years completed a baseline questionnaire on lifestyle, diet, and newly diagnosed diseases (22). The occupational selections were made to increase the cost-effectiveness of the studies and to improve internal validity by drawing on the participants' health-care backgrounds to obtain accurate health-related information. Biennial questionnaires were used to collect data on environmental and lifestyle factors and disease outcomes in both cohorts. The institutional review boards of Partners HealthCare System (Boston, Massachusetts) and Harvard School of Public Health (Boston, Massachusetts) approved this study. We considered the participants' completion and return of the self-administered questionnaires as provision of informed consent.

A total of 110,128 women in the NHS and 45,815 men in the HPFS returned a baseline questionnaire with questions on sunburn history (1982 in NHS; 1992 in HPFS). We excluded participants with a baseline history of melanoma or nonskin cancer and participants who had missing data on sunburn history. After exclusions, 87,166 women and 32,959 men remained in the present study.

Assessment of skin cancer cases

Participants reported new diagnoses of skin cancer (melanoma, SCC, or BCC) biennially. Medical and pathological reports were collected from participants who reported melanoma or SCC and were then reviewed by study physicians, who were unaware of exposure status, to retrieve information on tumor histology. For melanoma and SCC, in-situ cases were excluded from this analysis. Invasive cases of melanoma were further classified into 3 site-specific categories according to tumor location: head/neck, trunk, and limbs. Medical records were not obtained for BCC cases. However, a high accuracy of self-reported BCC among subsets of cohort participants has been demonstrated in previous validation studies, with approximately 90% being confirmed by histopathological findings or medical records (23, 24).

Assessment of sunburn history

In 1982, NHS participants responded to questions regarding their history of severe and painful sunburn and the number of such sunburns (never, 1–2 times, 3–5 times, or 6 or more times) they had had at each of the following body sites: face/arms, back/shoulder, and lower limbs. In 1992, HPFS participants were asked whether they had ever had a sunburn that blistered during their lifetime and how many times (never, 1–2 times, 3–5 times, 6–9 times, or 10 or more times) they had had such a sunburn at the following body sites: face, back/chest, and thighs/legs. We classified the 3 different body sites as face/arms (face/arms for women; face for men), trunk (back/shoulder for women; back/chest for men), and lower limbs (lower limbs for women; thighs/legs for men). For each body site, participants who reported never having had a sunburn at that site were classified as being without a history of sunburn at that body site, and those who reported having a sunburn in any other sunburn count category were classified as participants with a history of sunburn at that body site. The total number of severe sunburns was calculated as the sum of all sunburns that had occurred at the above 3 different body sites. For each sunburn category, the midpoint of the category was used to assign the number of sunburns for that category; for the highest category of severe sunburn in each cohort, we assigned a number that was 1 point higher than the cutoff number (e.g., 7 for "6 or more times" in women and 11 for "10 or more times" in men).

Assessment of covariates

In the biennial follow-up questionnaires, we inquired and updated information on anthropometric and lifestyle factors for chronic diseases, including body height and weight and physical activity. Information on dietary factors, including consumption of alcohol and caffeinated coffee, was collected using a validated food frequency questionnaire, starting in 1980 in the NHS and 1986 in the HPFS (21). Data on the following phenotypic and sun exposure related factors were also collected through the follow-up questionnaires (6, 25): ethnicity (Mediterranean, Scandinavian, other Caucasian, nonwhite, or other ancestry); family history of melanoma in first-degree relatives (parents, siblings, or offspring); natural hair color in early adulthood (age 21 years in women and age 18 years in men); number of moles with a diameter of ≥3 mm on arms; skin reaction after prolonged sun exposure as a child/adolescent; average amount of time spent in direct sunlight in the summer months since high school; and cumulative ultraviolet flux since baseline. Ultraviolet flux is an estimate of the amount of ultraviolet B radiation (wavelength range 290–315 nm) and the portion of ultraviolet A radiation (wavelength range 315–330 nm) reaching the earth's surface, as measured by a Robertson-Berger meter (26).

Statistical analysis

Participants contributed to follow-up time from the month of return of the baseline questionnaire (June 1982 for NHS; January 1992 for HPFS) to the month of the first diagnosis of any cancer (except KCs in analyses of melanoma), the month of death, or the end of follow-up (June 2010 for NHS; January 2010 for HPFS), whichever came first. To maintain statistical power, the models for risk of melanoma controlled for previous history of KC (SCC and BCC), whereas in analyses of SCC and BCC, women were censored upon a report of SCC, BCC, or another cancer diagnosis.

We used Cox proportional hazards models to estimate the age-adjusted and multivariable-adjusted hazard ratios and 95% confidence intervals for the outcome disease associated with baseline sunburn history (never/ever) and number of severe sunburns (0, 1–5, 6–10, 11–15, or ≥16 for total number of sunburns; 0, 1–2, 3–5, or ≥6 for number of sunburns at specific body sites). We also performed an analysis for history of sunburn at only 1 body site to test the separate associations for site-specific sunburns. Multivariable analyses were conducted with adjustment for age, host risk score (described below), history of KC (for melanoma), average amount of time spent in direct sunlight during the summer months since high school, cumulative ultraviolet flux since baseline, physical activity, alcohol intake, and caffeinated coffee intake. To avoid overadjustment, we created a host risk score for each participant using cohort-derived hazard ratios associated with each of the 5 host risk factors for skin cancer (i.e., family history of melanoma, natural hair color, number of moles on arms, skin reaction after prolonged sun exposure as a child/adolescent, and ethnicity) and then adjusted for it in the models as quintiles (27). We performed trend tests across number-of-sunburn categories by assigning median values for these categories and treating the new variables as continuous terms in the models. Heterogeneity between associations was examined by means of the Q statistic (28). Interaction between sunburn history and adjusted variables was examined using a likelihood ratio test. We used SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina), for all statistical analyses. All statistical tests were 2-tailed, and the significance level was set at $P < 0.05$.

RESULTS

We documented a total of 1,165 invasive melanomas over the course of follow-up (including 774 melanomas among women during 2,089,242 person-years of follow-up and 391 melanomas among men during 483,453 person-years of follow-up). We also documented 2,164 SCCs (1,366 in women and 798 in men) and 21,546 BCCs (16,092 in women and 5,454 in men) over the course of follow-up. In women, 83 melanomas (10.7%) occurred on the head/neck, 228 (29.5%) on the trunk, and 439 (56.7%) on the limbs; whereas in men, 117 melanomas (29.9%) occurred on the head/neck, 157 (40.2%) on the trunk, and 89 (22.8%) on the limbs. Participants with a higher number of sunburns appeared to be younger, were more likely to have a family history of melanoma and natural red/blonde hair, had a higher prevalence of arm moles and a painful burn/blistering skin reaction after prolonged sun exposure as a child/adolescent, were more likely to live in areas with a higher annual ultraviolet flux, and had higher alcohol intake (Table 1).

After adjustment for other risk factors, overall baseline history of severe sunburn was strongly associated with melanoma risk in both women and men in a dose-response manner, and the magnitude of the association appeared to be higher in men than in women (Table 2). Compared with participants who had never been sunburned, the multivariable-adjusted hazard ratios for melanoma were 1.63 (95% confidence interval (CI): 1.21, 2.20) for women who had ever been sunburned and 2.41 (95% CI: 1.32, 4.41) for men. Compared with the association with risk of melanoma, history of severe sunburn was associated with similarly increased risks of SCC and BCC in women (hazard ratios were 1.39 and 1.42, respectively) and, less apparently, increased risks of SCC and BCC in men (hazard ratios were 1.48 and 1.18, respectively). The heterogeneity among associations of melanoma, SCC, and BCC with overall history of severe sunburn reached statistical significance in men ($P = 0.04$) but not in women ($P = 0.66$). Further testing suggested that the heterogeneity in men was driven by the difference between melanoma and BCC ($P = 0.02$).

Among site-specific sunburn variables, sunburn on the trunk was most apparently associated with melanoma risk in stratified analysis among persons with sunburns at only 1 body site, particularly in men (Table 3). The multivariable-adjusted hazard ratios for melanoma in men were 2.33 (95% CI: 1.22, 4.45) for those who had sunburn on the trunk only, 1.84 (95% CI: 0.68, 4.99) for the face only, and 1.55 (95% CI: 0.49, 4.86) for lower limbs only. Heterogeneity for the difference between associations for site-specific sunburns and melanoma risk did not reach statistical significance in either women or men (all P's > 0.10), which may have been due to the limited number of melanoma cases. However, we found significant heterogeneity between associations for trunk sunburn and risks of melanoma and BCC ($P = 0.05$ in women and $P = 0.03$ in men). The heterogeneity between associations for trunk sunburn and risks of melanoma and SCC did not reach statistical significance (all P's > 0.10).

Further analyses using sunburn counts at different body sites as categorical variables in the entire study population supported the more apparent association of melanoma risk with sunburn on the trunk than with sunburn on the face/arms or lower limbs (Table 4). The heterogeneity among associations for melanoma with site-specific sunburns in the entire population was marginally significant in men ($P = 0.05$) but not in women ($P = 0.15$). Further tests suggested that there were statistically significant differences between associations with sunburn on the trunk and sunburn on the face ($P = 0.04$) and between associations with sunburn on the trunk and sunburn on the lower limbs ($P = 0.02$) in men; and the difference between associations with sunburn on the trunk and sunburn on the face was also marginally significant in women ($P = 0.05$). In addition, only sunburn on the trunk was still significantly associated with melanoma risk in both sexes in a joint model including 3 different site-specific sunburn variables simultaneously (data not shown).

In sensitivity analyses, we further adjusted for several other lifestyle and behavioral confounders, such as body mass index, smoking status, and sunscreen use in the summer months, and results remained essentially unchanged (data not shown).

Table 1. Baseline Characteristics of Study Participants According to Total Number of Severe Sunburns in the Nurses' Health Study (1982–2010) and the Health Professionals Follow-up Study (1992–2010)[a]

Sex and Characteristic	Total No. of Severe Sunburns									
	0		1–5		6–10		11–15		≥16	
	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%	No. or Mean (SD)	%
Women										
No. and % of participants	10,820	12.4	32,676	37.5	14,632	16.8	14,962	17.2	14,076	16.1
Age, years	49.6 (7.1)		48.7 (7.3)		47.8 (7.2)		47.7 (7.1)		47.6 (7.0)	
Family history of melanoma (first-degree relatives)		5.1		6.6		7.2		7.7		8.4
Red/blonde hair		7.8		12.1		15.5		19.0		25.3
Had moles on arm		28.2		35.7		38.4		39.8		40.7
Painful burn/blistering reaction to sunburn as a child/adolescent		0.7		6.2		14.2		21.5		37.5
Amount of time spent in direct sunlight in summer months since high school, hours/week	5.2 (3.0)		5.3 (2.9)		5.4 (2.9)		5.4 (2.9)		5.6 (2.9)	
Annual ultraviolet flux ($\times 10^{-4}$ Robertson-Berger count)[b]	121.1 (23.9)		120.9 (23.8)		121.8 (24.4)		123.0 (25.1)		124.0 (25.6)	
Physical activity level, metabolic equivalent-hours/week	14.7 (21.3)		14.3 (21.8)		13.3 (17.5)		13.8 (21.6)		14.0 (20.4)	
Alcohol intake, g/day	5.9 (10.5)		6.2 (10.9)		6.5 (11.0)		6.9 (11.3)		7.4 (11.7)	
Caffeinated coffee, cups/day	2.0 (2.0)		2.1 (2.0)		2.1 (2.0)		2.1 (2.0)		2.2 (2.1)	
Men										
No. and % of participants	2,809	8.5	13,958	42.3	5,152	15.6	3,940	12.0	7,100	21.5
Age, years	59.0 (9.9)		59.4 (9.7)		58.9 (9.6)		59.1 (9.4)		57.8 (8.7)	
Family history of melanoma (first-degree relatives)		4.2		4.4		4.4		5.5		5.1
Red/blonde hair		8.2		11.7		14.5		15.7		20.1
Had moles on arm		29.0		32.5		32.8		33.3		32.9
Painful burn/blistering reaction to sunburn as a child/adolescent		8.2		17.2		28.2		33.1		46.0
Amount of time spent in direct sunlight in summer months since high school, hours/week	10.1 (5.9)		9.8 (6.0)		10.1 (5.8)		10.3 (6.0)		10.9 (5.9)	
Annual ultraviolet flux ($\times 10^{-4}$ Robertson-Berger count)	127.5 (27.0)		128.8 (27.0)		131.3 (27.6)		131.3 (27.3)		134.7 (28.1)	
Physical activity level, metabolic equivalent-hours/week	37.1 (43.1)		35.7 (41.1)		35.8 (41.0)		38.3 (45.0)		38.8 (42.2)	
Alcohol intake, g/day	10.7 (14.5)		10.7 (13.9)		11.0 (14.3)		11.2 (14.7)		12.3 (15.5)	
Caffeinated coffee, cups/day	1.2 (1.4)		1.3 (1.4)		1.3 (1.5)		1.3 (1.5)		1.3 (1.5)	

[a] All values except age have been standardized to the age distribution of the study population. The total number of severe sunburns was calculated as the sum of the numbers of sunburns incurred on the face/arms, back/shoulder, and lower limbs for women and on the face, back/chest, and thighs/legs for men.

[b] Ultraviolet flux is an estimate of the amount of ultraviolet B radiation (wavelength range 290–315 nm) and the portion of ultraviolet A radiation (wavelength range 315–330 nm) reaching the earth's surface, as measured by a Robertson-Berger meter (26). Annual ultraviolet flux has a range of 93 $\times 10^{-4}$ to 196 $\times 10^{-4}$ Robertson-Berger count.

Table 2. Risk of Incident Skin Cancer According to Overall History of Severe Sunburn in the Nurses' Health Study (1982–2010) and the Health Professionals Follow-up Study (1992–2010)

Skin Cancer Type and No. of Severe Sunburns	Women						Men					
	No. of Cases	No. of Person-Years	Age-Adjusted		Multivariate-Adjusted[a]		No. of Cases	No. of Person-Years	Age-Adjusted		Multivariate-Adjusted[a]	
			HR	95% CI	HR	95% CI			HR	95% CI	HR	95% CI
Melanoma												
Never sunburned	47	256,347	1.00	Referent	1.00	Referent	11	40,907	1.00	Referent	1.00	Referent
No. of sunburns	727	1,832,895	2.20	1.63, 2.95	1.63	1.21, 2.20	380	442,546	3.21	1.76, 5.84	2.41	1.32, 4.41
1–5	253	781,410	1.78	1.31, 2.43	1.51	1.10, 2.06	139	202,629	2.56	1.38, 4.73	2.20	1.19, 4.07
6–10	120	352,994	1.89	1.35, 2.65	1.44	1.02, 2.02	62	75,895	3.04	1.60, 5.76	2.30	1.21, 4.39
11–15	138	362,456	2.13	1.53, 2.97	1.52	1.08, 2.12	53	58,086	3.39	1.77, 6.50	2.43	1.26, 4.67
≥16	216	336,036	3.60	2.63, 4.94	2.27	1.64, 3.13	126	105,936	4.50	2.43, 8.35	2.89	1.55, 5.39
P for trend				<0.001		<0.001				<0.001		<0.001
SCC												
Never sunburned	107	239,738	1.00	Referent	1.00	Referent	42	35,557	1.00	Referent	1.00	Referent
No. of sunburns	1,259	1,631,398	1.85	1.52, 2.25	1.39	1.13, 1.70	756	350,893	1.83	1.34, 2.50	1.48	1.08, 2.03
1–5	428	712,691	1.40	1.13, 1.73	1.20	0.97, 1.49	320	166,582	1.61	1.16, 2.22	1.43	1.03, 1.97
6–10	214	315,774	1.64	1.30, 2.07	1.27	1.00, 1.61	122	60,034	1.75	1.23, 2.49	1.43	1.00, 2.04
11–15	302	318,526	2.33	1.87, 2.91	1.71	1.36, 2.15	103	45,233	1.92	1.34, 2.75	1.49	1.04, 2.15
≥16	315	284,408	2.80	2.25, 3.49	1.89	1.50, 2.38	211	79,045	2.33	1.67, 3.25	1.66	1.18, 2.33
P for trend				<0.001		<0.001				<0.001		<0.001
BCC												
Never sunburned	1,311	239,738	1.00	Referent	1.00	Referent	377	35,557	1.00	Referent	1.00	Referent
No. of sunburns	14,781	1,631,398	1.76	1.66, 1.86	1.42	1.34, 1.51	5,077	350,893	1.36	1.23, 1.51	1.18	1.06, 1.32
1–5	5,268	712,691	1.40	1.32, 1.49	1.25	1.17, 1.33	2,226	166,582	1.25	1.12, 1.39	1.15	1.03, 1.28
6–10	2,803	315,774	1.75	1.64, 1.87	1.45	1.35, 1.55	867	60,034	1.37	1.21, 1.54	1.19	1.05, 1.35
11–15	3,171	318,526	1.98	1.86, 2.12	1.57	1.47, 1.68	665	45,233	1.38	1.21, 1.56	1.16	1.02, 1.32
≥16	3,539	284,408	2.51	2.36, 2.68	1.87	1.75, 2.00	1,319	79,045	1.59	1.42, 1.79	1.28	1.13, 1.44
P for trend				<0.001		<0.001				<0.001		<0.001

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma.

[a] Results of multivariate analyses were adjusted for age, host risk score[b] (no units; quintiles), history of keratinocyte carcinoma (for melanoma), average amount of time spent in direct sunlight during the summer months since high school (<2, 2–5, or ≥6 hours/week), cumulative ultraviolet flux since baseline ($\times 10^{-4}$ Robertson-Berger count; quintiles), physical activity (metabolic equivalent-hours/week; quintiles), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, or ≥20.0 g/day for women; 0, 0.1–9.9, 10–19.9, 20.0–29.9, or ≥30.0 g/day for men), and caffeinated coffee intake (0, <1, 1–2, or ≥3 cups/day).

[b] To avoid overadjustment, we created a host risk score for each participant using cohort-derived hazard ratios associated with each of the 5 host risk factors for skin cancer (i.e., family history of melanoma, natural hair color, number of moles on arms, skin reaction after prolonged sun exposure as a child/adolescent, and ethnicity) and then adjusted for it in the models as quintiles (27).

Table 3. Risk of Incident Skin Cancer According to History of Severe Sunburn at Only 1 Body Site in the Nurses' Health Study (1982–2010) and the Health Professionals Follow-up Study (1992–2010)

Skin Cancer Type and Site of Sunburn	Women						Men					
	No. of Cases	No. of Person-Years	Age-Adjusted		Multivariate-Adjusted[a]		No. of Cases	No. of Person-Years	Age-Adjusted		Multivariate-Adjusted[a]	
			HR	95% CI	HR	95% CI			HR	95% CI	HR	95% CI
Melanoma												
Never sunburned	47	256,347	1.00	Referent	1.00	Referent	11	40,907	1.00	Referent	1.00	Referent
Face/arms only	6	24,026	1.35	0.58, 3.16	1.18	0.51, 2.77	6	10,172	2.18	0.81, 5.90	1.84	0.68, 4.99
Trunk only	62	181,047	1.88	1.28, 2.74	1.65	1.13, 2.41	56	78,853	2.65	1.39, 5.06	2.33	1.22, 4.45
Lower limbs only	4	16,495	1.35	0.48, 3.74	1.15	0.41, 3.20	4	8,530	1.71	0.54, 5.38	1.55	0.49, 4.86
SCC												
Never sunburned	107	239,738	1.00	Referent	1.00	Referent	42	35,557	1.00	Referent	1.00	Referent
Face/arms only	14	21,937	1.42	0.81, 2.47	1.31	0.75, 2.28	16	8,196	1.63	0.91, 2.90	1.46	0.82, 2.60
Trunk only	102	166,979	1.40	1.06, 1.83	1.23	0.93, 1.61	118	65,562	1.49	1.05, 2.13	1.34	0.94, 1.90
Lower limbs only	11	15,058	1.65	0.89, 3.07	1.49	0.80, 2.78	11	7,090	1.29	0.66, 2.51	1.19	0.61, 2.31
BCC												
Never sunburned	1,311	239,738	1.00	Referent	1.00	Referent	377	35,557	1.00	Referent	1.00	Referent
Face/arms only	154	21,937	1.27	1.08, 1.50	1.19	1.00, 1.40	111	8,196	1.27	1.03, 1.58	1.19	0.96, 1.47
Trunk only	1,111	166,979	1.23	1.14, 1.34	1.12	1.04, 1.22	855	65,562	1.22	1.08, 1.38	1.13	1.00, 1.28
Lower limbs only	113	15,058	1.37	1.13, 1.66	1.26	1.04, 1.53	85	7,090	1.10	0.87, 1.39	1.04	0.82, 1.32

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma.

[a] Results of multivariate analyses were adjusted for the covariates listed in footnote "a" of Table 2.

Table 4. Risk of Incident Melanoma According to Number of Severe Sunburns at Different Body Sites in the Nurses' Health Study (1982–2010) and the Health Professionals Follow-up Study (1992–2010)

Body Site and No. of Severe Sunburns	Women						Men					
	No. of Cases	No. of Person-Years	Age-Adjusted		Multivariate-Adjusted[a]		No. of Cases	No. of Person-Years	Age-Adjusted		Multivariate-Adjusted[a]	
			HR	95% CI	HR	95% CI			HR	95% CI	HR	95% CI
Face/arms (women: face/arms; men: face only)												
Never sunburned	166	596,037	1.00	Referent	1.00	Referent	132	210,952	1.00	Referent	1.00	Referent
No. of sunburns	608	1,493,206	1.48	1.25, 1.76	1.16	0.98, 1.39	259	272,501	1.54	1.25, 1.90	1.25	1.01, 1.55
1–2	212	668,725	1.15	0.94, 1.41	1.01	0.82, 1.24	88	112,648	1.28	0.97, 1.67	1.16	0.88, 1.52
3–5	154	413,378	1.36	1.09, 1.69	1.08	0.86, 1.35	59	62,737	1.50	1.11, 2.04	1.23	0.90, 1.68
≥6	242	411,103	2.16	1.77, 2.63	1.49	1.21, 1.82	112	97,117	1.88	1.46, 2.42	1.35	1.04, 1.75
P for trend			<0.001		<0.001				<0.001		0.02	
Trunk (women: back/shoulder; men: back/chest)												
Never sunburned	60	308,798	1.00	Referent	1.00	Referent	22	64,231	1.00	Referent	1.00	Referent
No. of sunburns	714	1,780,444	2.10	1.61, 2.73	1.59	1.22, 2.08	369	419,223	2.60	1.69, 3.99	2.07	1.34, 3.20
1–2	247	721,333	1.78	1.34, 2.36	1.52	1.14, 2.02	116	157,766	2.17	1.38, 3.43	1.96	1.24, 3.10
3–5	191	562,030	1.79	1.34, 2.39	1.37	1.02, 1.84	93	118,322	2.30	1.44, 3.66	1.87	1.17, 2.98
≥6	276	497,081	2.94	2.22, 3.88	1.95	1.47, 2.60	160	143,136	3.33	2.13, 5.21	2.36	1.50, 3.71
P for trend			<0.001		<0.001				<0.001		0.002	
Lower limbs (women: lower limbs; men: thighs/legs)												
Never sunburned	160	627,912	1.00	Referent	1.00	Referent	110	170,946	1.00	Referent	1.00	Referent
No. of sunburns	614	1,461,330	1.68	1.41, 1.99	1.33	1.11, 1.59	281	312,508	1.39	1.11, 1.73	1.14	0.91, 1.43
1–2	264	750,294	1.40	1.15, 1.70	1.21	1.00, 1.48	115	147,850	1.20	0.92, 1.56	1.08	0.83, 1.40
3–5	172	420,958	1.64	1.32, 2.03	1.28	1.03, 1.59	68	83,860	1.24	0.92, 1.68	1.00	0.74, 1.36
≥6	178	290,078	2.45	1.98, 3.04	1.68	1.35, 2.10	98	80,798	1.89	1.44, 2.49	1.38	1.05, 1.83
P for trend			<0.001		<0.001				<0.001		0.01	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Results of multivariate analyses were adjusted for the covariates listed in footnote "a" of Table 2.

Models adjusting for 5 individual host risk factors instead of the host risk score yielded slightly attenuated risk estimates (data not shown). We tested whether the association between sunburn history and risk of skin cancer was modified by adjustment variables and did not find consistent modification between the two cohorts. Finally, sensitivity analyses with all KCs censored during follow-up for melanoma replicated the major findings as documented above (data not shown).

DISCUSSION

In the present study, we conducted a detailed evaluation of the association between history of severe sunburn and risk of 3 major skin cancers (melanoma, SCC, and BCC) on the basis of data from 2 prospective cohort studies of women and men. After extensive adjustment for other risk factors, we found that baseline history of severe sunburn was associated with risk of 3 different skin cancers in a dose-response manner, and that it was more closely associated with melanoma risk than with risk of SCC or BCC in men. Among the site-specific sunburns, sunburn on the trunk may be a better predictor of the risk of developing melanoma than sunburns at other body sites in both men and women.

Our finding that severe sunburn on the trunk may be a stronger predictor of melanoma risk than sunburn at other body sites is noteworthy, as previous studies usually treated sunburn as a general measure of intermittent sun exposure and did not account for the anatomical site of the sunburn (8–12). Sunburn is considered a biological marker for acute, high-dose ultraviolet radiation penetrating the protective layers of the epidermis down to the level of the melanocytes (11). It usually occurs after intense exposure to solar radiation within short periods of time and thus is considered an indicator of intermittent exposure. Its consistent relationship with melanoma risk is one of the factors contributing to the "intermittent exposure hypothesis" for melanoma (8). Our finding on the more apparent association of severe sunburn on the trunk with melanoma risk suggests that the association between history of sunburn and melanoma risk reported herein and in previous studies is probably driven by sunburn on the trunk. There may be several reasons for this. First, the trunk is less likely to be exposed to continuous solar radiation in comparison with the head/neck and limbs, and there is evidence for an inverse association of melanoma risk with a pattern of continuously high sun exposure (8). Second, participants who had ever been sunburned on the trunk would be more likely to have been exposed to episodes of intense solar radiation (e.g., outdoor recreational activities under direct sunlight) than those who had never been sunburned on the trunk or those who had only been sunburned on the head/neck or limbs. Third, the incidence of trunk melanoma has increased more rapidly than the incidence of other site-specific melanomas in the US population over the past several decades, which may be explained by an increasing prevalence of behaviors facilitating intermittent sun exposure (e.g., wearing bikinis and casual clothes with the trunk partially exposed to sunlight in summer) (29, 30).

In contrast to melanoma, risk of KC, especially SCC, is more closely associated with a pattern of continuously high sun exposure (6, 7, 31). Nevertheless, significant positive associations between sunburn history and risks of SCC and BCC have also been reported (13–15), whereas a direct comparison of the associations of sunburn history with 3 major skin cancers in the same study population has been unavailable to date. Our study suggested that severe sunburn appeared to be a stronger predictor of melanoma risk than of risk of SCC or BCC, particularly in men (Table 2). Furthermore, severe sunburns occurring at different body sites were similarly associated with risks of SCC and BCC, in contrast to the stronger associations with risk of melanoma (Tables 3 and 4). These results highlight the different disease etiologies of melanoma and KC associated with intermittent sun exposure (or intense exposure within short periods).

It is well known that sun exposure patterns differ between women and men, which may be responsible for the difference in the patterns of melanoma distribution by body site between the sexes (32). In particular, our data support lower melanoma rates on the limbs than on the rest of the body in men, while for women there is an excess risk of melanoma on the limbs. However, most previous studies of sunburn and melanoma did not provide sex-specific estimates (8, 9, 11) or only focused on 1 sex (10, 12), thereby hindering a detailed investigation of the sex difference. Given the differences in patterns of sun exposure and melanoma distribution by body site between women and men, a comparison of the associations for sunburn history and melanoma risk between women and men would be valuable for targeted prevention strategies tailored to the different sexes.

Our study had a number of strengths, including its prospective design, its large sample size, the long-term follow-up, the ability to include 3 major skin cancers simultaneously, the detailed ascertainment of melanoma cases with information on tumor location, and the ability to control for a number of skin cancer risk factors and potential confounders based on detailed cohort follow-up. These strengths are important for a more accurate assessment of the association between sunburn history and risk of melanoma and KC. Because NHS and HPFS were prospective studies, detailed information on history of severe sunburn was collected before the occurrence of outcome diseases (melanoma and KC); therefore, we could avoid the potential recall bias present in case-control studies. In addition, sunburn history may be associated with other skin cancer risk factors (e.g., host susceptibility, including family history of melanoma, mole count, hair color, and skin sensitivity) (33, 34), and some lifestyle and dietary variables (i.e., physical activity, alcohol and caffeinated coffee intakes) have also been associated with altered risk of melanoma and KC in recent years (17–21). Adjustment for these variables attenuated the risk estimates to an appreciable extent (Table 2).

Nevertheless, our study also had limitations. Although we collected detailed information on sunburn history at baseline, we did not have information on timing of sunburn occurrence (i.e., childhood or adulthood), which may be relevant to skin cancer risk (8, 12, 14). However, in a previous meta-analysis based on data over 30 studies, Gandini et al. (8) reported essentially similar pooled relative risks for melanoma in association with sunburns that occurred in childhood, adulthood, and "all life," which were 2.24, 1.92, and 2.08, respectively. Sunburn history was assessed once at baseline and the variable was not updated during follow-up, which may have introduced a

certain amount of measurement error. However, given that exposure information was collected before outcome assessment, any measurement error is likely to have been random and to have resulted in underestimation of risk estimates for the sunburn history–skin cancer association. In addition, the sunburn questions posed to women and men were not identical and may have introduced a difference in response patterns between women and men. Nevertheless, the generally consistent findings between the two cohorts (e.g., associations of site-specific sunburns with risk of melanoma as shown in Table 4) alleviate the concern about potential heterogeneity and highlight coherence in the relationship between sunburn and skin cancer among women and men.

In summary, our study found that baseline history of severe sunburn was more strongly associated with risk of developing melanoma than with risk of KCs (SCC and BCC) and that sunburn on the trunk appeared to predict melanoma risk more robustly than sunburns at other body sites in 2 sex-specific cohorts. These differences were more apparent in men than in women. These findings provide novel insights into the existing literature on sunburn history and risk of skin cancers and may have useful implications for the development of targeted prevention strategies for women and men. Specifically, persons who have ever been severely sunburned on the trunk may need to be aware of a potentially increased risk of developing melanoma. In clinical practice, physicians might also wish to pay more attention to those who have ever been severely sunburned on the trunk for early detection of melanoma.

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