Research Article

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Sun and Solarium Exposure and Melanoma Risk: Effects of Age, Pigmentary Characteristics, and Nevi

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Abstract

Background: Few prospective studies have analyzed solar and artificial (solarium) UV exposure and melanoma risk. We investigated these associations in a Norwegian-Swedish cohort study and addressed effect modification by age, pigmentary characteristics, and nevi.

Methods: The cohort included women ages 30 to 50 years at enrollment from 1991 to 1992. Host factors and exposure to sun and solariums in life decades were collected by questionnaire at enrollment. Relative risks (RR) with 95% confidence intervals (CI) were estimated by Poisson regression.

Results: Among 106,366 women with complete follow-up through 2005, 412 melanoma cases were diagnosed. Hair color and large, asymmetric nevi on the legs were strongly associated with melanoma risk ($P_{trend} < 0.001$), and the RR for ≥2 nevi increased from brown/black to blond/yellow to red-haired women (RRs, 1.72, 3.30, and 4.95, respectively; $P_{interaction} = 0.18$). Melanoma risk increased significantly with the number of sunburns and bathing vacations in the first three age decades ($P_{trend} \leq 0.04$) and solarium use at ages 30 to 39 and 40 to 49 years [RRs for solarium use ≥1 time/mo 1.49 (95% CI, 1.11-2.00) and 1.61 (95% CI 1.10-2.35), respectively; $P_{trend} \leq 0.02$]. Risk of melanoma associated with sunburns, bathing vacations, and solarium use increased with accumulating exposure across additional decades of life.

Conclusions: Melanoma risk seems to continue to increase with accumulating intermittent sun exposure and solarium use in early adulthood. Apparently, super-multiplicative joint effects of nevi and hair color identify people with red hair and multiple nevi as a very high risk group and suggest important gene-gene interactions involving *MC1R* in melanoma etiology. *Cancer Epidemiol Biomarkers Prev; 19(1); 111–20. ©2010 AACR.*

Introduction

Although solar UV exposure is the major established environmental risk factor for cutaneous malignant melanoma (hereafter called melanoma), the association is complex (1-3). Intermittent exposures such as outdoor recreation and bathing vacations, and sunburn, a marker of intermittent exposure, are risk factors for melanoma (2). Migration studies suggest that childhood is a sensitive period (3), whereas a recent meta-analysis concluded that melanoma risk increased with increasing number of sunburns in all life-periods (4). The association between indoor UV radiation (use of indoor tanning devices hereafter called solariums) and melanoma is still uncertain, with strongest evidence for exposure before age 35 (5). Host factors are important with number of nevi being the most powerful predictor of melanoma risk (1, 3). Pigmentary characteristics such as hair and eye color and the skin's sensitivity to sunburns and ability to tan also determine melanoma susceptibility (1, 6).

Interactions between these risk factors are also of interest because they may have implications for individual risk of melanoma. Hair color is a phenotypic indicator of the *MC1R* genotype that may modify the association between nevi and melanoma risk (7, 8). Nevi may be markers of etiologic heterogeneity in melanoma (9) and it has been hypothesized that the associations between sun and solarium exposure and melanoma risk are modified by the presence of asymmetric nevi (9, 10). Previous studies have mainly been concerned with effect modification of the association between UV exposure and melanoma risk by pigmentary characteristics, but no firm conclusion can yet be drawn (10-17).

Many case-control studies but few cohort studies have investigated melanoma risk factors (10, 18). We previously presented early results on UV exposure at ages 10 to 49 and melanoma risk in the Norwegian-Swedish Women's Lifestyle and Health Cohort Study with follow-up

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through 1999 (18). Our analyses indicated that young ages were the most sensitive periods for the effects of sunburn and solarium use but follow-up was relatively short for exposure at older ages. We now present results on sun and solarium exposure in five age decades with follow-up through 2005. The substantial growth in number of observed cases (from 187 to 412) now allows more informative analyses of main effects and interactions between risk factors (19, 20), and also of UV exposure at ages below 10 years recorded in a subset of the data (Norwegian women).

Materials and Methods

Study Population

Established in 1991 to 1992, the Norwegian-Swedish Women's Lifestyle and Health Cohort study has been described previously (18). In Norway, a nationwide random sample of 100,000 women (born 1943-1957) was drawn from the Norwegian National Population Register. In Sweden, a random sample of 96,000 women (born 1943-1962) residing in Uppsala Health Care Region (comprising about one-sixth of the Swedish population) was drawn from the Swedish National Population Register.

All women received an invitation letter. The letter requested written informed consent and contained a comprehensive questionnaire to be completed and returned in a prepaid envelope. Only those who consented were included in the study cohort. The national data inspection boards and responsible medical ethical committees approved the study.

Host Factors and UV Exposure Information

The questions relevant to the analysis presented here were identical in the two countries and have been previously described in detail (18). The participants were asked about their natural hair color (dark brown/black, brown, blond/yellow, or red), eye color (brown, gray/green, or blue), and the number of asymmetric nevi larger than 5 mm on their legs from toes to groin (0, 1, 2-3, 4-6, 7-12, 13-24, or ≥25 nevi). A color brochure with pictures of three examples of asymmetric nevi was enclosed. Participants also recorded how their skin reacts to heavy (acute) sun exposure at the beginning of the summer (turns brown without first becoming red, turns red, red with pain, or red with pain and blisters) and how their skin reacts to repeated and long-lasting (chronic) sun exposure (turns deep brown, brown, light brown, or never turns brown).

Participants reported their histories of UV exposure when they were 10 to 19, 20 to 29, 30 to 39, and 40 to 49 y old. For each age period, the participant was asked to report the number of times per year she had been burned by the sun so severely that it resulted in pain or blisters and subsequent peeling (never, ≤1, 2-3, 4-5, or ≥6 times/y), the average number of weeks per year spent on bathing vacations in southern latitudes or within Norway or Sweden (never, 1, 2-3, 4-6, or ≥7 wk/y), and the average use of a solarium (a sunbed or a sunlamp that emits artificial UV light—never, rarely, 1, 2, 3-4 times/mo, or >1 time/wk). In addition, the Norwegian questionnaire also included the above questions on sunburn, bathing vacations and solarium use for the age period 0 to 9 y. Finally, current height and weight, current and past contraceptive use, reproductive history, prevalent diseases and lifestyle habits were asked of all women.

Follow-up and End points

Start of follow-up was defined as the date of receipt of the returned questionnaire and end of follow-up was December 31, 2005. We calculated person-years from the start of follow-up to the date of diagnosis of primary melanoma, to the date of emigration or death, or to the end of follow-up, whichever occurred first. Cancer cases were identified by linkage to the national cancer registries in Norway and Sweden. Linkage to Statistics Norway and Statistics Sweden gave information on death and emigration. The individually unique national registration number assigned to all residents of Norway and Sweden ensured the linkages.

We have previously reported that 57,584 (57.6%) of the Norwegian women and 49,259 (51.3%) of the Swedish women returned completed questionnaires (18). All Swedish and 57,567 Norwegian women were available for analysis. We excluded 244 women who were diagnosed with melanoma prior to the start of follow-up, 4 women with inadequate information on vital status, 16 women who had emigrated or died before the start of follow-up, 1 woman who emigrated at the date for start of follow-up, and 195 women who did not adequately answer the questions regarding sun exposure or personal characteristics (sun sensitivity of skin, hair color, eye color, and number of asymmetric nevi). Thus, 106,366 women were included in the analyses presented here.

Statistical Methods

We defined four categories of region of residence: the southern, middle, and northern regions of Norway, and the Uppsala Health Care Region in Central Sweden (18). Due to small numbers, the upper two (most sun-sensitive) categories were combined for the variables concerning skin reaction to acute and chronic exposure to the sun; we analyzed nevus counts in four categories: 0, 1, 2 to 6, and ≥7; and in the analyses of sunburns, bathing vacations, and use of a solarium during different decades of life, we also collapsed higher categories of each variable. In addition, for sunburns, bathing vacations, and use of a solarium, we combined the exposure across each of the three decades of life that were recorded for all women (10-19, 20-29, and 30-39 y).

Calendar year of solarium use is important because exposure before 1982/1983 is likely to be from tanning devices with UVB-rich mercury arc lamps whereas exposure after 1982/1983 would be predominantly from

modern sunbeds with UVA-rich fluorescent lamps. In our cohort, ages 20 to 29 y are most informative for distinguishing exposure in these two periods (21). We constructed four categories by combining the use of a solarium at age 20 to 29 (never, rarely, and ≥1 time/mo) and the calendar years in which women were ages 20 to 29 (1963-1991): never, ≥1 time/mo and 20 to 29 y old in 1979 to 1991, ≥1 time/mo and 20 to 29 y old in 1975 to 1987, and ≥1 time/mo and 20 to 29 y old in 1963 to 1983 (women rarely exposed were omitted).

We used one-way ANOVA to compare sites of melanoma with regard to age at diagnosis. Poisson regression analysis was used to estimate the association between melanoma risk and personal characteristics, sunburns, bathing vacations, or use of a solarium. We analyzed trends across categories of a variable by assigning equally spaced values (e.g., 1, 2, 3, or 4) to the categories and treating the variable as a continuous variable in the regression analysis. All analyses were adjusted for attained age categorized in 5-y intervals (for analysis of women ages ≥40 at inclusion, we used 40-49, 50-54, and ≥55). All multivariable models included geographic region of residence. Multivariable models used in the analyses of personal characteristics also included hair color and skin reaction to acute and chronic sun exposure (if not being the characteristic under study). Analyses of sunburns, bathing vacations, and use of a solarium were also adjusted for pigmentary characteristics (hair color and skin reaction to acute and chronic sun exposure). Additionally, each age-specific model for use of a solarium included the age-specific sunburns and sunbathing vacations.

A likelihood ratio test was used to test the statistical significance of interaction effects. Personal characteristics were dichotomized when included in an interaction term—hair color (black/brown or blond/yellow/red), skin reaction to acute sun exposure (brown/red or red with pain/red with pain and blisters), skin reaction to chronic sun exposure (deep brown/brown or light brown/never brown), and large, asymmetric nevi on the legs (0 or ≥1)—except when a 3 × 3 interaction was studied for large, asymmetric nevi (0, 1, or ≥2) and hair color (black/brown, blond/yellow, or red). For sunburns, bathing vacations, and solarium use, we analyzed interactions using dichotomous cumulative exposure variables for ages 10 to 39 y: exposure above the baseline category in any of the three decades compared with baseline exposure in all decades.

All statistical analyses were conducted in STATA (version 10). Results are presented as relative risks (RR) with 95% confidence intervals (CI). All P values were two-sided and a 5% level of significance was used.

Results

In the final study cohort of 106,366 women, the mean age at study entry was 40.4 years (range, 30-50 years), average follow-up was 14 years (range, 0.01-14.6 years), and mean age at diagnosis was 49.2 years (range, 31-63 years). During 1,489,298 person years of observation, a total of 412 incident cases of melanoma were reported to the cancer registries in Norway and Sweden. Each was the woman's first diagnosis of melanoma: it was also the first cancer diagnosis for 394 women, the second for 15 and the third for 3. The lower limbs were the commonest site of melanoma (n = 171), followed by the trunk (n = 112), upper limbs (n = 64), other (n = 41), and head/neck (n = 24). Age at diagnosis did not differ between the sites (P = 0.63). Fifty-two percent of melanomas were classified as superficial spreading melanoma (n = 216), 12% nodular melanoma (n = 51), 1% lentigo malignant melanoma (n = 3), and 35% as malignant melanoma not otherwise specified (n = 142).

Pigmentary Characteristics and Large, Asymmetric Nevi

We found a strong association between hair color and melanoma risk (Table 1). In an analysis adjusted for attained age and region of residence, the risk was approximately 2-fold higher for women with blond hair and 4-fold higher for women with red hair, relative to women with dark brown or black hair. The risk of melanoma also increased significantly with increasing sensitivity of the skin to both acute and chronic sun exposure ($P_{trend} < 0.001$). After mutual adjustment for the three pigmentary characteristics, only hair color remained statistically significant (Table 1). We found no interaction between hair color and skin reaction after acute sun exposure ($P_{interaction}$ = 0.88), hair color and skin reaction after chronic sun exposure ($P_{interaction}$ = 0.33), or between skin reaction after acute and after chronic sun exposure ($P_{interaction}$ = 0.33). Eye color was not associated with melanoma risk (Table 1).

We found a strong positive association between the number of asymmetric nevi larger than 5 mm on the legs and risk of melanoma both in age-adjusted and multivariable analyses (Table 2). The proportion with one or more large, asymmetric nevi on the legs was largest among red-haired women regardless of whether they were diagnosed with melanoma (46% among red-haired, 25% among blond or yellow-haired, 19% among brown-haired, and 17% among dark brown or black-haired), or not (20% among red-haired, 13% among blond or yellow-haired, 14% among brown-haired, and 13% among dark brown or black-haired). Our data suggest there is a super-multiplicative interaction between large, asymmetric nevi and hair color in the etiology of melanoma (i.e., the RR in women with the highest level of exposure for both variables is greater than the product of the RRs for the highest levels of the two variables considered individually; ref. 22). The RR among women with two or more large, asymmetric nevi on the legs compared with no nevi showed a gradient from 1.72 (95% CI, 1.03-2.89) in brown or black-haired women to 3.30 (95% CI, 2.15-5.06) in blond or yellow-haired women to 4.95 (95% CI, 1.88-13.01) in red-haired women ($P_{interaction}$ = 0.18; Table 2).

Table 1. RRs and 95% CIs for cutaneous malignant melanoma according to sun sensitivity characteristics

Characteristic	Frequencies no. (%)	No. of cases	Age-adjusted RR (95% CI)	Multivariable* RR (95% CI)	Multivariable† RR (95% CI)
Hair color (n = 101,998)					
Dark brown, black	22,802 (22)	47	1.00	1.00	1.00
Brown	42,081 (41)	148	1.70 (1.22-2.36)	1.66 (1.19-2.30)	1.54 (1.11-2.15)
Blond, yellow	34,145 (34)	173	2.45 (1.78-3.39)	2.29 (1.65-3.17)	2.07 (1.48-2.90)
Red	2,970 (3)	24	3.93 (2.40-6.43)	3.85 (2.35-6.30)	3.37 (2.02-5.64)
			P_{trend} < 0.001	P_{trend} < 0.001	P_{trend} < 0.001
Skin color after heavy sun exposure in the beginning of the summer (n = 101,998)					
Brown	25,483 (25)	71	1.00	1.00	1.00
Red	49,174 (48)	199	1.46 (1.12-1.92)	1.46 (1.12-1.92)	1.23 (0.92-1.64)
Red with pain/red with pain and blisters	27,341 (27)	122	1.66 (1.24-2.22)	1.68 (1.25-2.25)	1.33 (0.96-1.84)
			P_{trend} = 0.001	P_{trend} < 0.001	P_{trend} = 0.10
Skin color after repeated and long-lasting sun exposure (n = 101,998)					
Deep brown	16,616 (16)	38	1.00	1.00	1.00
Brown	60,676 (60)	242	1.74 (1.23-2.45)	1.75 (1.24-2.46)	1.38 (0.96-1.98)
Light brown/never brown	24,706 (24)	112	1.98 (1.37-2.86)	1.97 (1.36-2.84)	1.28 (0.85-1.93)
			P_{trend} < 0.001	P_{trend} < 0.001	P_{trend} = 0.54
Eye color (n = 100,990)					
Brown	12,743 (13)	43	1.00	1.00	1.00
Gray, green, or mix	37,557 (37)	146	1.13 (0.81-1.59)	1.10 (0.78-1.54)	0.85 (0.60-1.21)
Blue	50,580 (50)	195	1.13 (0.81-1.58)	1.10 (0.79-1.54)	0.79 (0.56-1.12)
			P_{trend} = 0.56	P_{trend} = 0.63	P_{trend} = 0.21

NOTE: Poisson regression analysis. All statistical tests were two-sided.
*Multivariable models included attained age and region of residence.
†Multivariable models included attained age, region of residence, hair color and skin color after heavy sun exposure in the beginning of the summer and after repeated sun exposure.

We found no similar interaction between large, asymmetric nevi and skin reaction after acute ($P_{interaction}$ = 0.51) or chronic sun exposure ($P_{interaction}$ = 0.44).

Sunburns

There were significant positive trends in melanoma risk with number of sunburns during ages <10, 10 to 19, and 20 to 29 and the RRs were 1.67, 1.92, and 1.62, respectively, for two or more sunburns per year as compared with none (Table 3). The positive trend was much weaker following sunburns at age 30 to 39 years and not evident at all for sunburns at age 40 to 49 years.

We then combined information about sunburns during the three decades from age 10 to 39 years, which were recorded for all women. Compared with none or only one sunburn per year in all three age decades, the RR increased from 1.48 for two or more sunburns per year as a teenager to 1.69 for two or more sunburns per year in all three decades, suggesting that sunburns repeated over successive decades increases risk (P_{trend} < 0.001; Table 3). Significant excess risk was also observed for sunburns in adult age only (RR, 1.57; Table 3). We found no significant interactions between a dichotomous cumulative sunburn variable and hair color ($P_{interaction}$ = 0.29), skin reaction after acute ($P_{interaction}$ = 0.81) or chronic sun exposure ($P_{interaction}$ = 0.46), or number of large, asymmetric nevi on the legs ($P_{interaction}$ = 0.23).

Bathing Vacations

There were significant positive trends in melanoma risk with number of bathing vacations to southern latitudes or within Norway and Sweden during ages <10, 10 to 19, and 20 to 29 years and women with four or more weeks per year of bathing vacations had a RR of 1.50, 1.87, and 1.59, respectively, as compared with women with no bathing vacations (Table 4). Some evidence of increased risk was also found for ages 30 to 39 years, but not for ages 40 to 49 years.

Only 2% of all women reported bathing vacations solely in teenage years, whereas 45% reported bathing vacations in all the three age decades between 10 and 39 years (Table 4). The latter group had a RR of 1.54 compared with women with no bathing vacations in all three age decades. No significant interactions were found between a dichotomous cumulative variable for bathing vacations and hair color ($P_{interaction}$ = 0.61), skin reaction after acute

($P_{interaction}$ = 0.41) or chronic sun exposure ($P_{interaction}$ = 0.81), or the number of large, asymmetric nevi on the legs ($P_{interaction}$ = 0.28).

Solariums

Only 0.4% and 2% of the women in the cohort had used a solarium at ages <10 and 10 to 19 years, respectively (only Norwegian women had information for age <10 years). For solarium use at ages 20 to 29, 30 to 39, and 40 to 49 years, the risks of melanoma were 1.53, 1.49, and 1.61, respectively, for use once or more per month as compared with never and the trend was significant for the last two age periods (Table 5).

Compared with no use of a solarium in the three decades from 10 to 39 years, the RRs increased from 1.24 for rarely use one, two, or three decades to 1.38 for use one or more times per month in one of the three decades to 2.37 for use one or more times per month in two or three decades (P_{trend} = 0.003; Table 5). Dichotomization gave RR, 1.31 (95% CI, 1.03-1.66; P = 0.03) for ever versus never solarium use at ages 10 to 39 years. No significant interactions were found between this cumulative variable for use of solariums and hair color ($P_{interaction}$ = 0.28), skin reaction after acute ($P_{interaction}$ = 0.96), or chronic sun exposure ($P_{interaction}$ = 0.15), the number of large, asymmetric nevi on the legs ($P_{interaction}$ = 0.91), sunburn ($P_{interaction}$ = 0.26), or bathing vacations ($P_{interaction}$ = 0.79).

We then combined solarium exposure at ages 20 to 29 with calendar years. Despite the fact that the total number of melanoma cases had now more than doubled since our previous analyses (21), this analysis added little information because the number of cases only increased from 18 to 25 among women who reported using a solarium ≥1 time/mo at ages 20 to 29 (results not shown).

Discussion

We have prospectively studied risk of melanoma in relation to host factors and sun and solarium exposure, and their possible interactions. Hair color and the number of large, asymmetric nevi on the legs were strongly associated with melanoma risk. Skin response to acute and chronic sun exposure and eye color were only weakly associated with risk and their associations seemed to be largely accounted for by that of hair color. The number of large, asymmetric nevi on the legs was more strongly associated with melanoma among women with red, blond, or yellow hair than in those with brown or black hair. Both for sunburns and bathing vacations, melanoma risk increased with exposure accumulated over successive decades from ages 10 to

Table 2. RRs and 95% CIs for cutaneous malignant melanoma according to the number of asymmetric nevi >5 mm on the legs (97,151 women)

	No. of nevi	Frequencies	No. of cases	Age-adjusted	Multivariable*
		No. (%)		RR (95% CI)	RR (95% CI)
	0	83,381 (86)	278	1.00	1.00
	1	7,987 (8)	42	1.60 (1.15-2.21)	1.64 (1.19-2.28)
	2-6	4,957 (5)	35	2.15 (1.51-3.05)	2.17 (1.52-3.09)
	≥7	826 (1)	14	5.24 (3.06-8.96)	5.01 (2.92-8.61)
				P_{trend} < 0.001	P_{trend} < 0.001
Hair color					
Brown or black hair	0	53,370	149	1.00	1.00†
	1	5,145	20	1.41 (0.88-2.24)	1.46 (0.91-2.33)
	≥2	3,488	16	1.66 (0.99-2.79)	1.72 (1.03-2.89)
Blond, yellow hair	0	27,811	119	1.00	1.00
	1	2,564	18	1.65 (1.00-2.71)	1.72 (1.04-2.82)
	≥2	1,966	26	3.14 (2.05-4.79)	3.30 (2.15-5.06)
Red hair	0	2,200	10	1.00	1.00
	1	278	4	3.17 (1.00-10.12)	3.31 (1.04-10.55)
	≥2	329	7	4.78 (1.82-12.57)	4.95 (1.88-13.01)
					$P_{interaction}$ = 0.18

NOTE: Poisson regression analysis. All statistical tests were two-sided.

*Multivariable models included attained age, region of residence, hair color, skin color after heavy sun exposure in the beginning of the summer and skin color after repeated sun exposure.

†In addition to the covariates mentioned above, the model included the interaction between asymmetric nevi >5 mm on the legs and hair color.

Table 3. RRs and 95% CIs for cutaneous malignant melanoma according to annual number of sunburns in successive decades of age

Age period and number of sunburns	Frequencies No. (%)	No. of cases	Age-adjusted RR (95% CI)	Multivariable* RR (95% CI)
<10 y (n = 45,707)				
0	19,114 (42)	67	1.00	1.00
≤1/y	21,043 (46)	104	1.41 (1.04-1.92)	1.23 (0.90-1.69)
≥2/y	5,550 (12)	42	2.18 (1.48-3.20)	1.67 (1.10-2.54)
			P_{trend} < 0.001	P_{trend} = 0.02
10-19 y (n = 94,695)				
0	21,417 (23)	52	1.00	1.00
≤1/y	52,125 (55)	203	1.65 (1.21-2.23)	1.39 (1.01-1.91)
≥2/y	21,153 (22)	111	2.32 (1.67-3.22)	1.92 (1.34-2.74)
			P_{trend} < 0.001	P_{trend} < 0.001
20-29 y (n = 96,660)				
0	20,008 (21)	60	1.00	1.00
≤1/y	58,102 (60)	217	1.28 (0.96-1.70)	1.13 (0.83-1.52)
≥2/y	18,550 (19)	97	1.86 (1.34-2.56)	1.62 (1.14-2.31)
			P_{trend} < 0.001	P_{trend} = 0.004
30-39 y (n = 94,077)				
0	30,166 (32)	109	1.00	1.00
≤1/y	53,900 (57)	212	1.08 (0.85-1.36)	0.99 (0.77-1.26)
≥2/y	10,011 (11)	52	1.44 (1.03-2.00)	1.29 (0.91-1.83)
			P_{trend} = 0.06	P_{trend} = 0.28
40-49 y (n = 44,772)				
0	19,687 (44)	91	1.00	1.00
≤1/y	22,129 (49)	101	0.98 (0.74-1.30)	0.89 (0.66-1.20)
≥2/y	2,956 (7)	9	0.65 (0.33-1.30)	0.57 (0.29-1.16)
			P_{trend} = 0.38	P_{trend} = 0.14
Combined, 10-39 y (n = 89,753)†				
≤1/y, 10-19, 20-29, and 30-39 y	64,241 (72)	215	1.00	1.00
≥2/y, 10-19 y only	7,304 (8)	39	1.66 (1.18-2.34)	1.48 (1.05-2.10)
≥2/y, 10-19 and 20-29 y	6,251 (7)	30	1.72 (1.20-2.48)	1.63 (1.12-2.36)
≥2/y, 10-19, 20-29, and 30-39 y	6,112 (7)	36	1.76 (1.23-2.51)	1.69 (1.17-2.46)
			P_{trend} < 0.001	P_{trend} < 0.001
≥2/y, 20-29 and/or 30-39 y	5,845 (7)	30	1.57 (1.07-2.29)	1.57 (1.07-2.31)

NOTE: Poisson regression analysis. All statistical tests were two-sided. Sunburns at age <10 y was only recorded for the Norwegian women. Analyses of sunburns at ages 40-49 y included only women ≥40 y when answering the questionnaire.

*Multivariable models included attained age, region of residence, hair color and skin color after heavy sun exposure in the beginning of the summer and after repeated sun exposure.

†Combined variable for sunburns at ages 10 to 39 years. Women with ≥2 sunburns per year at ages 10 to 19 and 30 to 39 were not included (n = 176). Test for trend is restricted to categories with extension of exposure into successive decades of life.

39 years. Melanoma risk also increased following solarium use in early and middle adult life and with cumulative solarium use over age decades 10 to 39 years. None of these effects were appreciably modified by hair color, skin reaction to sun exposure, or number of large, asymmetric nevi on the legs.

Our findings for hair color are consistent with the summary RR in a recent meta-analysis (6) in which association with skin type, skin color, and eye color were lower than for hair color, but statistically significant. Associations between melanoma and pigmentary characteristics might vary between populations (e.g., ref. 23, 24) and we hypothesized that hair color may be the best measure of sun sensitivity in Scandinavia and other fair-skinned populations (18).

Asymmetric nevi larger than 5 mm on the legs was a strong host risk factor of melanoma, in agreement with other studies from Europe, the United States, and Australia (1, 25). The assessment of asymmetric (atypical/dysplastic) nevi has varied between studies (presence, ordinal categories, or continuous) and most studies have recorded counts on the arms or the whole body

(7, 25, 26). Self-reporting, as in our study, has limited accuracy for the diagnosis of one or more dysplastic nevi and may overestimate its prevalence (27). We found that 14% of the cohort (14% of noncases and 25% of cases) had at least one large asymmetric nevus on the legs whereas Titus-Ernstoff et al. (9) found that 14% of controls (and 39% of the cases) had clinical evidence of at least one atypical nevus on the whole body in men

Table 4. RRs and 95% CIs for cutaneous malignant melanoma according to annual number of weeks per year spent on bathing vacations to southern latitudes or within Norway or Sweden in successive decades of age

Age period and number of bathing vacations	Frequencies	No. of cases	Age-adjusted	Multivariable*
	No. (%)		RR (95% CI)	RR (95% CI)
<10 y (n = 47,111)				
0	35,693 (76)	160	1.00	1.00
1 wk/y	3,437 (7)	17	1.17 (0.71-1.93)	1.11 (0.67-1.83)
2-3 wk/y	4,533 (10)	27	1.40 (0.93-2.11)	1.34 (0.89-2.02)
≥4 wk/y	3,448 (7)	24	1.58 (1.03-2.42)	1.50 (0.97-2.32)
			P_{trend} = 0.02	P_{trend} = 0.04
10-19 y (n = 92,655)				
0	44,787 (48)	172	1.00	1.00
1 wk/y	19,834 (21)	72	1.04 (0.79-1.37)	1.12 (0.84-1.48)
2-3 wk/y	19,973 (22)	72	1.05 (0.80-1.39)	1.12 (0.84-1.48)
≥4 wk/y	8,061 (9)	49	1.74 (1.27-2.40)	1.87 (1.35-2.58)
			P_{trend} = 0.01	P_{trend} = 0.003
20-29 y (n = 95,228)				
0	26,041 (27)	91	1.00	1.00
1 wk/y	28,564 (30)	119	1.28 (0.97-1.68)	1.35 (1.02-1.78)
2-3 wk/y	32,814 (35)	127	1.20 (0.92-1.58)	1.27 (0.97-1.67)
≥4 wk/y	7,809 (8)	35	1.43 (0.97-2.11)	1.59 (1.07-2.37)
			P_{trend} = 0.10	P_{trend} = 0.03
30-39 y (n = 93,039)				
0	23,884 (26)	79	1.00	1.00
1 wk/y	28,684 (31)	126	1.34 (1.01-1.78)	1.39 (1.05-1.85)
2-3 wk/y	32,965 (35)	137	1.26 (0.96-1.66)	1.31 (0.99-1.73)
≥4 wk/y	7,506 (8)	33	1.34 (0.89-2.01)	1.47 (0.97-2.21)
			P_{trend} = 0.13	P_{trend} = 0.06
40-49 y (n = 44,713)				
0	13,500 (30)	60	1.00	1.00
1 wk/y	12,714 (28)	63	1.10 (0.77-1.56)	1.16 (0.81-1.66)
≥2-3 wk/y	18,499 (41)	81	0.97 (0.69-1.35)	1.01 (0.72-1.42)
			P_{trend} = 0.80	P_{trend} = 0.99
Combined, 10-39 y (n = 86,869)†				
0, 10-19, 20-29, and 30-39 y	15,460 (18)	52	1.00	1.00
≥1/y, 10-19 y only	1,729 (2)	4	0.77 (0.28-2.14)	0.81 (0.29-2.57)
≥1/y, 10-19 and 20-29 y	2,720 (3)	9	1.16 (0.57-2.36)	1.27 (0.62-2.58)
≥1/y, 10-19, 20-29, and 30-39 y	39,254 (45)	171	1.41 (1.03-1.93)	1.54 (1.12-2.12)
			P_{trend} = 0.02	P_{trend} = 0.006
≥1/y, 20-29 and/or 30-39 y	27,706 (32)	116	1.26 (0.91-1.75)	1.29 (0.93-1.80)

NOTE: Poisson regression analysis. All statistical tests were two-sided. Bathing vacations at age <10 y was only recorded for the Norwegian women. Analyses of bathing vacations at ages 40 to 49 y included only women ≥40 y when answering the questionnaire.

*Multivariable models included attained age, region of residence, hair color and skin color after heavy sun exposure in the beginning of the summer and after repeated sun exposure.

†Combined variable for bathing vacations at ages 10 to 39 years. Women with ≥1 bathing vacations per year at ages 10 to 19 and 30 to 39 were not included (n = 872). Test for trend is restricted to categories with extension of exposure into successive decades of life.

Table 5. RRs and 95% CIs for cutaneous malignant melanoma according to solarium use in successive decades of age

Age period and solarium use	Frequencies No. (%)	No. of cases	Age-adjusted RR (95% CI)	Multivariable* RR 95% CI
10-19 y (n = 85,210)				
Never	83,554 (98)	326	1.00	1.00
Rarely or ≥1 time/mo	1,656 (2)	7	1.30 (0.61-2.75)	1.19 (0.56-2.53)
			P_{trend} = 0.51	P_{trend} = 0.66
20-29 y (n = 88,478)				
Never	70,550 (80)	279	1.00	1.00
Rarely	11,560 (13)	41	1.15 (0.81-1.61)	1.08 (0.77-1.53)
≥1 time/mo	6,368 (7)	25	1.39 (0.90-2.14)	1.53 (0.99-2.38)
			P_{trend} = 0.13	P_{trend} = 0.09
30-39 y (n = 87,219)				
Never	43,863 (50)	166	1.00	1.00
Rarely	28,243 (32)	119	1.23 (0.96-1.56)	1.14 (0.89-1.45)
≥1 time/mo	15,113 (17)	71	1.41 (1.06-1.87)	1.49 (1.11-2.00)
			P_{trend} = 0.01	P_{trend} = 0.01
40-49 y (n = 41,022)				
Never	17,063 (42)	68	1.00	1.00
Rarely	14,449 (35)	65	1.12 (0.79-1.57)	1.14 (0.81-1.62)
≥1 time/mo	9,510 (23)	51	1.34 (0.93-1.93)	1.61 (1.10-2.35)
			P_{trend} = 0.12	P_{trend} = 0.02
Combined, 10-39 y (n = 79,042)				
Never in all decades, 10-39 y	37,991 (48)	137	1.00	1.00
Rarely but not ≥1 time/mo in any decade, 10-39 y	26,599 (34)	114	1.36 (1.05-1.75)	1.24 (0.96-1.61)
≥1 time/mo in one decade, 10-39 y	11,576 (15)	48	1.33 (0.95-1.86)	1.38 (0.98-1.94)
≥1 time/mo in two or three decades, 10-39 y	2,876 (4)	16	2.13 (1.25-3.64)	2.37 (1.37-4.08)
			P_{trend} = 0.004	P_{trend} = 0.003

NOTE: Poisson regression analysis. All statistical tests were two-sided. Analyses of solarium use at ages 40 to 49 y included only women ≥40 y when answering the questionnaire.

*Multivariable models included attained age, region of residence, pigmentation characteristics (hair color and skin color after heavy sun exposure in the beginning of the summer and after repeated sun exposure) and solar exposure (corresponding number of age-specific sunburns and weeks on annual bathing vacations).

and women in New Hampshire. Similar whole body prevalences were observed in Australia (15%) and England (9%; ref. 28).

Red-haired women were more likely to have large, asymmetric nevi on the legs than women with other hair colors. Higher nevus count for red-haired women was reported recently among young English women (29), but other studies of adults did not find this (30), or rather concluded the opposite (31, 32). Our data suggest the possibility of a super-multiplicative interaction between large, asymmetric nevi and hair color with the RR for two or more large, asymmetric nevi on the legs relative to no nevi increasing from 1.72 in brown/black-haired women to 3.30 in blond/yellow-haired women and 4.95 in red-haired women. This is in accordance with a pooled analysis of case-control studies that showed higher risk of melanoma associated with high nevus counts among women with red hair than for women with freckling but no red hair or women without these phenotypes (7). The pooled study used hair color and freckling as a proxy for *MC1R* genotype status. Melanoma risk associated with *MC1R* allelic variants may be modified by many nevi or presence of clinically atypical nevi (8).

Recent meta-analyses reported increased risk with increasing number of sunburns during all life-periods (4), with no significant differences between sunburns in childhood and adulthood (2). Sunburns during different life-periods were not independent, but were related to skin type and UV exposure; susceptible individuals may have learned to avoid sunburns in adult life (4, 11). We found similarly significant effects of sunburns before age 30, but no convincing effects following sunburns during the subsequent two decades, possibly due to insufficient follow-up time. Importantly, RRs increased with exposure in successive decades from 10 to 39 years.

Sunburns in teenage years only and sunburns after age 20 only were both associated with significantly increased risk. As in the Nurses' Health Study, sunburn was positively confounded by sun sensitivity (12), probably because, to some degree, they measure the same characteristics, acute sensitivity to the sun and experience of intense intermittent sun exposure, although differently weighted.

For bathing vacations, we also found significant positive trends only following exposure before age 30, again possibly due to insufficient lag period for later exposure. The assessment of intermittent exposure varies considerably between studies (2). We recorded bathing vacations to southern latitudes as well as within Norway and Sweden in one variable, which may represent a wide range of UV exposure. A recent test-retest study within the Norwegian cohort found that during the last 5 years sunbathing vacations to southern latitudes had better reproducibility than sunbathing vacations in Norway or outside southern latitudes (33).

Solarium use is positively associated with melanoma, but the evidence is strongest for use before 35 years of age and insufficient regarding dose-response relationships (5). In our cohort, use of a solarium was rare before age 20 and a previous analysis showed a higher excess risk following exposure at ages 20 to 29 than at ages 30 to 49 years (18). With longer follow-up, we found similar effects following exposure in the entire age-span 20 to 49 years, and a clear positive trend for cumulative use of solariums at age 10 to 39 years. Previous studies have also found little confounding by sun exposure (5, 12, 15).

Sweden and Norway implemented similar national regulations for indoor tanning devices in 1982 and 1983, respectively, and the UVB-rich sunlamps were replaced with UVA-rich fluorescent lamps. The regulations were not revised until late in 1992. The UVA and UVB irradiances of approved tanning devices in Norway varied little between 1982/1983 and 1992 (34). In this cohort, exposure at ages 20 to 29, 30 to 39, and 40 to 49 years corresponds to exposure in 1962 to 1991, 1972 to 1992, and 1982 to 1992, respectively. Thus, solarium users in the first two age periods were exposed to UVB-rich sunlamps until about 1982/1983 and then UVA-rich sunbeds. Because solarium use at ages 40 to 49 took place after the regulations in 1982/1983 it implies exposure to UVA-rich solariums. However, the effect of solarium use in this decade was similar to those in the two preceding decades, which is consistent with a meta-analysis indicating that the excess melanoma risk is not limited to the use of earlier types of indoor tanning appliances (5). Our direct analysis of effects of exposure before and after 1982/1983 had too few additional cases to change the results we presented earlier (21).

The effects of sunburns, bathing vacations, and solarium use were not modified by hair color, skin response to acute or chronic sun exposure, or large, asymmetric nevi on the legs. Real interactions may go undetected because the test for interaction lacks power (35). To increase power, we have tested interactions with binary variables combining UV exposure groups at ages 10 to 39 years. In the Nurses' Health Study, a significant interaction was found between constitutional susceptibility and sun exposure while wearing a bathing suit, with the RR higher in those with highest susceptibility (12), but other studies did not report significant interaction effects between UV exposure and sun sensitivity (10, 11, 13, 14, 17). As regards indoor tanning, previous studies did not find interactions between sunbed/sunlamp use and pigmentary characteristics (14, 15) or change in results when restricting analysis of sunbed use to sun-sensitive subjects (36). In a Swedish study, however, the association between sunbed use and melanoma risk was stronger for individuals with black/dark brown or light brown hair than for individuals with blond/fair or red hair (16).

Our results add materially to the very limited evidence from cohort studies that increasing intermittent pattern sun exposure and use of solariums increase melanoma risk. Importantly, it also suggests that intermittent sun exposure and solarium use in successive early decades of life add to previous exposure in increasing melanoma risk. Reduction in either exposure in adult life should, therefore, lead to a reduction in melanoma risk. There was little indication that the relative effects of intermittent sun exposure or solarium use varied with hair color, cutaneous sun sensitivity, or presence of asymmetric large nevi. These observations are consistent with multiplicative joint effects and suggest that the effects of UV exposure on melanoma risk are greater in absolute terms in those with high-risk phenotypes than those with low-risk phenotypes. Probably most important is the evidence we found of super-multiplicative joint effects of hair color and asymmetric large nevi, identifying people with red hair and asymmetric large nevi as having a very high risk of melanoma. This finding is consistent with a recent report of a similar interaction of *MC1R* red hair variants with many nevi or the presence of clinically atypical nevi and suggests there are important gene-gene interactions involving *MC1R* that should be investigated.

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No potential conflicts of interest were disclosed.

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