JAMA Dermatology | Original Investigation

Association of Phenotypic Characteristics and UV Radiation Exposure With Risk of Melanoma on Different Body Sites

Reza Ghiasvand, PhD; Trude E. Robsahm, PhD; Adele C. Green, PhD; Corina S. Rueegg, PhD; Elisabete Weiderpass, PhD; Eiliv Lund, PhD; Marit B. Veierød, PhD

IMPORTANCE Two pathways have been hypothesized for the development of cutaneous melanoma: one typically affects the head and neck, a site with chronic sun damage, and the other affects the trunk, which is less exposed to the sun. However, the possible cause of limb melanomas is less studied under this hypothesis.

OBJECTIVE To investigate the association between phenotypic characteristics, pattern of UV radiation exposure, and risk of melanoma on different body sites.

DESIGN, SETTING, AND PARTICIPANTS This study used data on 161 540 women with information on phenotypic characteristics and UV radiation exposure who were part of the Norwegian Women and Cancer study, a population-based prospective study established in 1991 with exposure information collected by questionnaires at baseline and every 4 to 6 years during follow-up through 2015. Data analysis was performed from October 2017 through May 2018.

EXPOSURES Participants reported hair color, eye color, untanned skin color, number of small symmetric and large asymmetric nevi, and freckling, as well as histories of sunburns, sunbathing vacations, and indoor tanning in childhood, adolescence, and adulthood.

MAIN OUTCOMES AND MEASURES The Norwegian Women and Cancer study was linked to the Cancer Registry of Norway for data on cancer diagnosis and date of death or emigration. Primary melanoma site was categorized as head and neck, trunk, upper limbs, and lower limbs.

RESULTS During follow-up of the 161 540 women in the study (mean age at study entry, 50 years [range, 34-70 years]; mean age at diagnosis, 60 years [range, 34-87 years]), 1374 incident cases of melanoma were diagnosed. Having large asymmetric nevi was a significant risk factor for all sites and was strongest for the lower limbs (relative risk [RR], 3.38; 95% CI, 2.62-4.38) and weakest for the upper limbs (RR, 1.96; 95% CI, 1.22-3.17; $P = .02$ for heterogeneity). Mean lifetime number of sunbathing vacations was significantly associated with risk of trunk melanomas (RR, 1.14; 95% CI, 1.07-1.22) and lower limb melanomas (RR, 1.12; 95% CI, 1.05-1.19) but not upper limb melanomas (RR, 0.98; 95% CI, 0.88-1.09) and head and neck melanomas (RR, 0.87; 95% CI, 0.73-1.04; $P = .006$ for heterogeneity). Indoor tanning was associated only with trunk melanomas (RR for the highest tertile, 1.49; 95% CI, 1.16-1.92) and lower limb melanomas (RR for the highest tertile, 1.33; 95% CI, 1.00-1.76; $P = .002$ for heterogeneity). Skin color, hair color, small symmetric nevi, and history of sunburns were associated with risk of melanoma on all sites.

CONCLUSIONS AND RELEVANCE These results appear to support the hypothesis of divergent pathways to melanoma and that recreational sun exposure and indoor tanning are associated with melanoma on the lower limbs, the most common site of melanoma in women. These findings appear to have important preventive implications.

JAMA Dermatol. 2019;155(1):39-49. doi:10.1001/jamadermatol.2018.3964
Published online November 21, 2018.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Reza Ghiasvand, PhD, Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, PO Box 1122 Blindern, N-0317 Oslo, Norway (reza.ghiasvand@medisin.uio.no).

The incidence of cutaneous melanoma (hereafter, *melanoma*), has increased markedly in many fair-skinned populations during the past decades.[1] Melanoma was responsible for approximately 1.6 million years of healthy life lost globally in 2015, with the greatest burden in New Zealand, Australia, Europe, and North America.[2] Excessive sun exposure is the foremost preventable risk factor and is responsible for most melanomas.[3] However, the association between sun exposure and melanoma is complex,[4,5] and individual risk also depends on pigmentary characteristics, such as hair color, ability to develop a tan, and the type and number of nevi,[5-7] which in turn are associated with inherited genetic factors, age, and sun exposure.[8,9]

Two pathways have been hypothesized for the development of melanoma.[10,11] One typically affects areas of the skin with long-term sun exposure, such as the head and neck in older individuals (age, >55 years) with few melanocytic nevi. The other pathway arises primarily on areas less exposed to the sun, such as the trunk in younger individuals with multiple melanocytic nevi.[12]

A number of epidemiologic studies that compared individuals with trunk melanoma vs head and neck melanoma support the existence of divergent pathways in melanoma development,[13-15] although some studies did not.[16-19] Moreover, the possible cause of limb melanomas is less studied under this hypothesis; because the lower limbs are the most common sites of melanoma among women, clarifying this cause is important for prevention. In addition, even though it is known that artificial UV radiation (UVR) causes melanoma,[20-23] the pathways to melanomagenesis after indoor tanning have not been explored, to our knowledge. We therefore examined the association between phenotypic characteristics, pattern of UVR exposure, and melanoma risk on different body sites using information from the large, population-based, prospective Norwegian Women and Cancer (NOWAC) cohort study.

Key Points

Question Do phenotypic characteristics and pattern of UV radiation exposure differ according to body site of melanoma?

Findings In this population-based cohort study, associations with large asymmetric nevi, sunbathing vacations, and indoor tanning differed significantly among melanoma sites. Skin color, hair color, small symmetric nevi, residential ambient UV radiation, and sunburns were associated with melanoma risk on all sites.

Meaning This study adds to the supporting evidence of divergent pathways to melanoma and suggests similar risk profiles for lower limb and trunk melanomas and for upper limb and head and neck melanomas.

Methods

The NOWAC Cohort

The NOWAC study was established in 1991. A nationwide random sample of more than 300 000 women aged 30 to 75 years was drawn from the National Population Register; 171 725 women (response rate, 54%) completed and returned the baseline questionnaire from 1991 to 2007 and received follow-up questionnaires every 4 to 6 years. Details on the NOWAC study and the design have been published previously.[24] Reproducibility of self-reported melanoma risk factors in the NOWAC study was good or acceptable and was independent of age, educational level, or skin color.[25] The Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics approved the study, and all participants provided written informed consent.

Follow-up and End Points

The unique identity number of Norwegian citizens was used to link individuals from the NOWAC study to the Cancer Registry of Norway for information on cancer (diagnosis date and histopathologic characteristics) and date of death or emigration. Primary tumor site was categorized using *International Classification of Diseases, Seventh Revision*, codes as head and neck (190.0), trunk (190.1 and 190.7), upper limbs (190.2), lower limbs (190.3 and 190.4), other (190.5, 190.6, and 190.8), and skin unspecified (190.9). Reporting of incident cancers to the Cancer Registry of Norway is compulsory, and 99.9% of melanomas are morphologically verified.[26]

Phenotypic Characteristics

Participants reported color of hair (dark brown and black, brown, blond and yellow, or red), eyes (brown; green, gray, or mixed; or blue), and untanned skin (recorded from 1 [very fair] to 10 [very dark] and categorized as very dark [9-10], dark [7-8], medium [4-6], and light [1-3]). Participants also reported the number of asymmetric nevi larger than 5 mm on their legs (recorded as 0, 1, 2-3, 4-6, 7-12, 13-24, and ≥25 and categorized as 0, 1, and ≥2; a color brochure with pictures of 3 examples of asymmetric nevi was provided) and freckling after sunbathing (yes or no). Subsamples of the cohort were asked about the number of small symmetric nevi on their legs or arms (categorized together as 0, 1-10, 11-50, and ≥50).

UVR Exposure

Residential ambient UVR was categorized according to region-specific cumulated doses of UV-B as low (northern Norway), medium-low (central Norway), medium (southwestern Norway), and highest (southeastern Norway).[27] Participants reported history of severe sunburns (never, 1, 2-3, 4-5, and ≥6 times per year), mean number of weeks spent on sunbathing vacations (never, 1, 2-3, 4-6, and ≥7 weeks per year), and mean use of an indoor tanning device (never; rarely; 1, 2, and 3-4 times per month; and >1 time per week) in childhood (age, ≤9 years), adolescence (age, 10-19 years), and adulthood (age, >19 years).

We summed and categorized the mean number of sunburns before age 20 years and at ages 20 to 49 years as none, 1 or fewer, and more than 1 per year. We further calculated mean annual lifetime number of sunburns by dividing the cumulative number of burns by age. Likewise, we summed and categorized the mean number of weeks spent on sunbathing vacations before age 20 years and at ages 20 to 49 years as none, 1 or fewer, and more than 1 week per year, and calculated mean

annual lifetime number of weeks on sunbathing vacations. Indoor tanning history was categorized as never use or ever use, and cumulative number of tanning sessions was calculated and categorized as never and in the following tertiles for users: lowest (≤14 sessions), medium (15-30 sessions), and highest (≥31 sessions) tertile.[21] A subsample of women (n = 66 300) was asked if they work outdoors professionally (yes or no). Sunscreen use in Norway or other high latitude countries and low latitude countries was collected by questionnaire as described in detail previously and was categorized as none, sun protection factor less than 15, and sun protection factor of 15 or more.[28]

Study Sample

Information on phenotypic characteristics and UVR exposure was collected for 162 834 women at baseline (eFigure in the Supplement). We excluded 290 participants with very dark skin (grades 9-10), 915 women with prevalent melanoma or squamous cell carcinoma of the skin, and 89 women who died or emigrated before the date of questionnaire return, resulting in 161 540 women for the analysis.

Statistical Analysis

Poisson regression analysis was used to estimate relative risks (RRs) and 95% CIs for overall and site-specific risk of melanoma, according to phenotypic characteristics and UVR exposure. A standard competing risk framework was used for each site. Person-years were calculated from date of baseline questionnaire to date of diagnosis, emigration, death, or the end of follow-up (December 31, 2015), whichever occurred first. Lifetime number of sunburns, weeks of sunbathing vacations, and cumulative number of indoor tanning sessions were included as time-varying variables in all models. Multinomial logistic regression was used and odds ratios and 95% CIs were calculated to compare age at diagnosis and tumor characteristics by site.

All analyses were adjusted for attained age and birth cohort. In the multivariable analyses of phenotypic characteristics, we adjusted for skin color, hair color, number of large asymmetric nevi, freckling, and residential UVR exposure. Additional adjustments for education and sunscreen use did not change the results. In the analyses of UVR exposures, models included skin and hair color, educational level, and residential UVR exposure. Additional adjustment for large asymmetric nevi, freckling, and sunscreen use did not change the results.

We tested for trend by treating the variable as continuous in the model. Interactions between host factors, number of nevi, and sun exposure are suggested in the literature.[12,29] We tested for interactions between hair color, the most important host factor for melanoma in this cohort,[30] and small symmetric nevi, large asymmetric nevi, and freckling, as well as between sunbathing and large asymmetric nevi and small symmetric nevi, using a likelihood ratio test. We tested whether exposure-disease associations differed among the sites by a contrast test (test for heterogeneity).[31] For covariates with missing information, missing values were treated as a separate category and were included in the models. All *P* values were 2-sided and results were deemed to be statistically significant at $P < .05$. Stata, version 14 (Stata Corp), was used in all analyses.

Results

During 2 682 000 person-years of follow-up (median, 18.0 years), 1374 women were diagnosed with a primary invasive melanoma. Mean age at study entry was 50 years (range, 34-70 years) and at diagnosis was 60 years (range, 34-87 years). The lower limb was the most common site of melanoma (n = 520), followed by the trunk (n = 461), upper limb (n = 219), head and neck (n = 110), and other and unspecified (n = 64) (**Table 1**). Mean age at diagnosis was lowest for the lower limb (59 years [range, 34-85 years]) and highest for head and neck (64 years [range, 42-84 years]). In particular, 27.3% of head and neck melanomas (30 of 110) and 15.5% of upper limb melanomas (34 of 219) were diagnosed in the eighth decade of life; corresponding proportions were 8.7% for the lower limb (45 of 520) and 10.0% for the trunk (46 of 461) (Table 1 and eTable 1 in the Supplement). The proportion of superficial spreading melanoma was higher for trunk and lower limb melanomas compared with head and neck and upper limb melanomas (Table 1 and eTable 1 in the Supplement). Breslow thickness was comparable among the 4 body sites (eTable 1 in the Supplement).

Phenotypic Characteristics

Lighter skin color was associated with significantly increased risk of melanoma overall and at all body sites (trunk: RR, 2.32; 95% CI, 1.50-3.58; $P < .001$ for trend; lower limb: RR, 1.61; 95% CI, 1.14-2.30; $P = .002$ for trend; upper limb: RR, 2.22; 95% CI, 1.14-4.31; $P = .03$ for trend; and head and neck: RR, 1.53; 95% CI, 0.75-3.11; $P = .04$ for trend), with no statistically significant variation by site ($P = .84$ for heterogeneity) (**Table 2**). Similarly, red hair was associated with significantly increased melanoma risk across all sites (trunk: RR, 3.30; 95% CI, 2.09-5.21; $P < .001$ for trend; lower limb: RR, 4.70; 95% CI, 3.11-7.11; $P < .001$ for trend; upper limb: RR, 4.97; 95% CI, 2.65-9.30; $P < .001$ for trend; and head and neck: RR, 2.50; 95% CI, 1.09-5.73; $P = .05$ for trend; $P = .62$ for heterogeneity). Freckling was significantly associated with melanoma overall (RR, 1.31; 95% CI, 1.15-1.48) and melanoma of upper limbs (RR, 1.43; 95% CI, 1.05-1.96) and lower limbs (RR, 1.42, 1.17-1.43), but with no significant difference by site ($P = .35$ for heterogeneity). Having large asymmetric nevi was also a significant risk factor for all body sites; association was strongest for lower limbs (RR, 3.38; 95% CI, 2.62-4.38) and weakest for upper limbs (RR, 1.96; 95% CI, 1.22-3.17) ($P = .02$ for heterogeneity). Small symmetric nevi were associated with melanoma on all body sites alike (trunk: RR, 3.48; 95% CI, 2.42-5.00; $P < .001$ for trend; lower limb: RR, 2.49; 95% CI, 1.80-3.45; $P < .001$ for trend; upper limb: RR, 2.19; 95% CI, 1.28-3.74; $P < .001$ for trend; and head and neck: RR, 2.56; 95% CI, 1.24-5.29; $P = .004$ for trend; $P = .31$ for heterogeneity). We found no significant interactions between hair color and number of large asymmetric or small symmetric nevi or freckling ($P = .09$ and $P = .70$ for interaction), although indications of joint effects were found for light hair color and both large and small nevi (eTable 2 in the Supplement).

Table 1. Host and Tumor Characteristics Among Women With Incident Melanoma in the Norwegian Women and Cancer Study by Body Site, 1991-2015

Characteristic	No. (%)				
	Total[a] (N = 1310)	Trunk (n = 461)	Lower Limb (n = 520)	Upper Limb (n = 219)	Head and Neck (n = 110)
Age at enrollment, y					
30-39	168 (12.8)	58 (12.6)	73 (14.0)	30 (13.7)	7 (6.4)
40-49	551 (42.1)	190 (41.2)	228 (43.8)	88 (40.2)	45 (40.9)
50-59	411 (31.4)	155 (33.6)	167 (32.1)	58 (26.5)	31 (28.2)
≥60	180 (13.7)	58 (12.6)	52 (10.0)	43 (19.6)	27 (24.5)
Age at diagnosis, y					
<50	139 (10.6)	37 (8.0)	76 (14.6)	17 (7.8)	9 (8.2)
50-59	448 (34.2)	175 (38.0)	181 (34.8)	64 (29.2)	28 (25.5)
60-69	568 (43.4)	203 (44.0)	218 (41.9)	104 (47.5)	43 (39.1)
≥70	155 (11.8)	46 (10.0)	45 (8.7)	34 (15.5)	30 (27.3)
Educational level, y					
≤9	240 (18.3)	81 (17.6)	95 (18.3)	39 (17.8)	25 (22.7)
10-12	449 (34.3)	167 (36.2)	175 (33.7)	71 (32.4)	36 (32.7)
≥13	554 (42.3)	190 (41.2)	226 (43.5)	97 (44.3)	41 (37.3)
Missing	67 (5.1)	23 (5.0)	24 (4.6)	12 (5.5)	8 (7.3)
Skin color					
Dark	79 (6.0)	23 (5.0)	37 (7.1)	10 (4.6)	9 (8.2)
Medium	497 (37.9)	180 (39.0)	196 (37.7)	87 (39.7)	34 (30.9)
Light	512 (39.1)	184 (39.9)	198 (38.1)	80 (36.5)	50 (45.5)
Missing	222 (16.9)	74 (16.1)	89 (17.1)	42 (19.2)	17 (15.5)
Eye color					
Brown	126 (9.6)	43 (9.3)	52 (10.0)	21 (9.6)	10 (9.1)
Green, gray, or mixed	488 (37.3)	153 (33.2)	199 (38.3)	88 (40.2)	48 (43.6)
Blue	661 (50.5)	253 (54.9)	256 (49.2)	102 (46.6)	50 (45.2)
Missing	35 (2.7)	12 (2.6)	13 (2.5)	8 (3.7)	2 (1.8)
Hair color					
Black or dark brown	140 (10.7)	50 (10.8)	50 (9.6)	21 (9.6)	19 (17.3)
Brown	397 (30.3)	137 (29.7)	161 (31.0)	70 (32.0)	29 (26.4)
Blond or yellow	646 (49.3)	236 (51.2)	258 (49.6)	100 (45.7)	52 (47.3)
Red	96 (7.3)	29 (6.3)	41 (7.9)	18 (8.2)	8 (7.3)
Missing	31 (2.4)	9 (2.0)	10 (1.9)	10 (4.6)	2 (1.8)
Freckling when sunbathing					
No	604 (46.1)	225 (48.8)	230 (44.2)	92 (42.0)	57 (51.8)
Yes	508 (38.8)	173 (37.5)	217 (41.7)	83 (37.9)	35 (31.8)
Missing	198 (15.1)	63 (13.7)	73 (14.0)	44 (20.1)	18 (16.2)
Large asymmetric nevi on legs, No.					
0	898 (68.5)	331 (71.8)	337 (64.8)	154 (70.3)	76 (69.1)
1	128 (9.8)	33 (7.2)	74 (14.2)	16 (7.3)	5 (4.5)
≥2	158 (12.1)	54 (11.7)	72 (13.8)	19 (8.7)	13 (11.8)
Missing	126 (9.6)	43 (9.3)	37 (7.1)	30 (13.7)	16 (14.5)
Small symmetric nevi on arms and legs, No.					
0	62 (4.7)	17 (3.7)	22 (4.2)	14 (6.4)	9 (8.2)
1-10	206 (15.7)	61 (13.2)	85 (16.3)	39 (17.8)	21 (19.1)
11-50	277 (21.1)	102 (22.1)	106 (20.4)	48 (21.9)	21 (19.1)
≥51	165 (12.6)	62 (13.4)	69 (13.3)	22 (10.0)	12 (10.9)
Missing	600 (45.8)	219 (47.5)	238 (45.8)	96 (43.8)	47 (42.7)

(continued)

Table 1. Host and Tumor Characteristics Among Women With Incident Melanoma in the Norwegian Women and Cancer Study by Body Site, 1991-2015 (continued)

Characteristic	No. (%)				
	Total[a] (N = 1310)	Trunk (n = 461)	Lower Limb (n = 520)	Upper Limb (n = 219)	Head and Neck (n = 110)
Melanoma subtype					
SSM	816 (62.3)	308 (66.8)	347 (66.7)	118 (53.9)	43 (39.1)
NM	187 (14.3)	58 (12.6)	68 (13.1)	45 (20.5)	16 (14.5)
LMM	35 (2.7)	3 (0.7)	3 (0.6)	6 (2.7)	23 (20.9)
Other[b]	268 (20.5)	91 (19.7)	102 (19.6)	48 (21.9)	27 (24.5)
Missing	4 (0.3)	1 (0.2)	0	2 (0.9)	1 (0.9)
Breslow thickness, mm					
<0.80	489 (37.3)	183 (39.7)	186 (35.8)	82 (37.4)	38 (34.5)
0.80-1.00	230 (17.6)	81 (17.6)	100 (19.2)	39 (17.8)	10 (9.1)
1.01-2.00	214 (16.3)	63 (13.7)	91 (17.5)	39 (17.8)	21 (19.1)
2.01-4.00	135 (10.3)	49 (10.6)	54 (10.4)	22 (10.0)	10 (9.1)
>4.00	46 (3.5)	19 (4.1)	15 (2.9)	7 (3.2)	5 (4.5)
Missing	196 (15.0)	66 (14.3)	74 (14.2)	30 (13.7)	26 (23.6)

Abbreviations: LM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.

[a] Excluding other and unspecified melanomas (n = 64).

[b] Other subtypes and melanoma not otherwise specified.

UVR Exposure

Compared with women with trunk or lower limb melanomas, a higher proportion of women diagnosed with upper limb or head and neck melanomas reported no sunbathing vacations or never use of indoor tanning devices during adulthood (**Figure**). For number of sunburns, proportions were comparable for all women (Figure). Similar patterns were observed for sunburns, sunbathing, and indoor tanning before age 20 years.

Living in lower latitudes in Norway was associated with increased melanoma risk on all sites (trunk: RR, 2.45; 95% CI, 1.80-3.35; $P < .001$ for trend; lower limb: RR, 2.60; 95% CI, 1.92-3.52; $P < .001$ for trend; upper limb: RR, 1.57; 95% CI, 1.08-2.30; $P = .05$ for trend; and head and neck: RR, 2.15; 95% CI, 1.18-3.94; $P = .02$ for trend; $P = .22$ for heterogeneity) (**Table 3**). Having outdoor work was significantly associated with increased risk of head and neck melanoma (RR, 2.07; 95% CI, 1.06-4.04; $P = .21$ for heterogeneity). We found no significant difference by site for history of sunburns before age 20 years, before 20 years and 20 to 49 years combined, and mean lifetime sunburns.

History of sunbathing vacations before age 20 years was significantly associated with lower limb melanoma (RR, 1.72; 95% CI, 1.35-2.18; $P < .001$ for trend) but not other sites (trunk: RR, 1.24; 95% CI, 0.95-1.62; upper limb: RR, 1.01, 95% CI, 0.66-1.54; and head and neck: RR, 0.58; 95% CI, 0.30-1.11; $P = .007$ for heterogeneity). Moreover, when combining histories of sunbathing before age 20 years and 20 to 49 years, the highest category of exposure was associated with increased risk of trunk (RR, 1.71; 95% CI, 1.06-2.76) and lower limb melanomas (RR, 1.67; 95% CI, 1.13-2.47) and decreased risk of head and neck melanoma (RR, 0.41; 95% CI, 0.18-0.93; $P = .002$ for interaction). Mean lifetime number of weeks of sunbathing vacation was also associated with significantly increased risk of trunk (RR, 1.14; 95% CI, 1.07-1.22) and lower limb melanomas (RR, 1.12; 95% CI, 1.05-1.19), but not with upper limb melanomas (RR, 0.98; 95% CI, 0.88-1.09) and head and neck melanomas (RR, 0.87; 95% CI, 0.73-1.04); ($P = .006$ for heterogeneity). We found no significant interaction between sunbathing and large asymmetric or small symmetric nevi ($P > .10$ and $P < .89$ for interaction).

Women reporting ever engaging in indoor tanning had significantly increased melanoma risk overall (RR, 1.18; 95% CI, 1.02-1.29) (Table 3). We found significant dose-response associations between cumulative number of indoor tanning sessions and risk of trunk (RR for highest tertile, 1.33; 95% CI, 1.00-1.76) and lower limb melanomas (RR for highest tertile, 1.49; 95% CI, 1.16-1.92) but not upper limb (RR for highest tertile, 1.00; 95% CI, 0.67-1.47) and head and neck melanomas (RR for highest tertile, 0.70; 95% CI, 0.39-1.26; $P = .002$ for heterogeneity).

Discussion

In this large population-based cohort study, associations with number of large asymmetric nevi, history of sunbathing vacations, and history of indoor tanning differed significantly among melanoma sites. Site-specific associations were also found for outdoor work and freckling but with no significant heterogeneity among sites. Skin color, hair color, number of small symmetric nevi, residential ambient UVR exposure, and history of sunburns were associated with increased melanoma risk on all sites.

Lower limb and trunk melanomas were significantly associated with younger age at diagnosis and were more likely to be superficial spreading melanoma (less likely to be nodular or lentigo maligna melanoma), in contrast with head and neck and upper limb melanomas; this finding agreed with the divergent pathways hypothesis and previous reports.[32] Unlike other reports of head and neck melanoma being thickest,[13] we found no significant difference in thickness among sites.

The melanocortin-1 receptor is one of the pigmentation genes responsible for pigment variation in humans.[33] The melanocortin-1 receptor is highly polymorphic in white individuals, and the variants determine phenotypic characteristics, such

Table 2. Risk of Melanoma Overall and Site-Specific Risk of Melanoma According to Phenotypic Characteristics Among 161 540 Women

Characteristic	RR (95% CI)[a]					P Value for Heterogeneity[b]
	Total (N = 1310)	Trunk (n = 461)	Lower Limb (n = 520)	Upper Limb (n = 219)	Head and Neck (n = 110)	
Skin color						
Dark	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	.84
Medium	1.44 (1.26-2.02)	1.78 (1.16-2.75)	1.23 (0.87-1.75)	1.96 (1.02-3.77)	0.86 (0.41-1.79)	
Light	1.89 (1.49-2.39)	2.32 (1.50-3.58)	1.61 (1.14-2.30)	2.22 (1.14-4.31)	1.53 (0.75-3.11)	
P value for trend	<.001	<.001	.002	.03	.04	NA
Hair color						
Black or dark brown	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	.62
Brown	1.25 (1.03-1.52)	1.20 (0.87-1.66)	1.42 (1.03-1.95)	1.48 (0.91-2.41)	0.70 (0.39-1.25)	
Blond or yellow	1.97 (1.64-2.37)	2.01 (1.48-2.72)	2.20 (1.63-3.00)	2.05 (1.29-3.28)	1.20 (0.71-2.01)	
Red	3.94 (3.03-5.10)	3.30 (2.09-5.21)	4.70 (3.11-7.11)	4.97 (2.65-9.30)	2.50 (1.09-5.73)	
P value for trend	<.001	<.001	<.001	<.001	.06	NA
Freckling after sunbathing						
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	.35
Yes	1.31 (1.15-1.48)	1.22 (0.99-1.51)	1.42 (1.17-1.73)	1.43 (1.05-1.96)	0.98 (0.63-1.52)	
Large asymmetric nevi on legs, No.						
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	.02
1	1.77 (1.47-2.13)	1.19 (0.81-1.76)	2.72 (2.11-3.50)	1.28 (0.77-2.14)	0.84 (0.34-2.08)	
≥2	2.83 (2.38-3.35)	2.67 (1.96-3.63)	3.38 (2.62-4.38)	1.96 (1.22-3.17)	2.85 (1.57-5.18)	
P value for trend	<.001	<.001	<.001	.005	.008	NA
Small symmetric nevi on arms and legs, No.						
0	0.63 (0.48-0.85)	0.56 (0.33-0.97)	0.56 (0.35-0.89)	0.61 (0.33-1.14)	0.72 (0.33-1.59)	.31
1-10	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	
11-50	1.51 (1.26-1.80)	1.96 (1.43-2.70)	1.39 (1.04-1.86)	1.58 (1.03-2.42)	1.38 (0.75-2.55)	
≥51	2.50 (2.04-3.08)	3.48 (2.42-5.00)	2.49 (1.80-3.45)	2.19 (1.28-3.74)	2.56 (1.24-5.29)	
P value for trend	<.001	<.001	<.001	<.001	.004	NA

Abbreviations: NA, not applicable; RR, relative risk.

[a] Poison regression analysis adjusted for attained age, birth cohort, skin color, hair color, large asymmetric nevi on legs, freckling after sunbathing, and residential ambient UV radiation exposure.

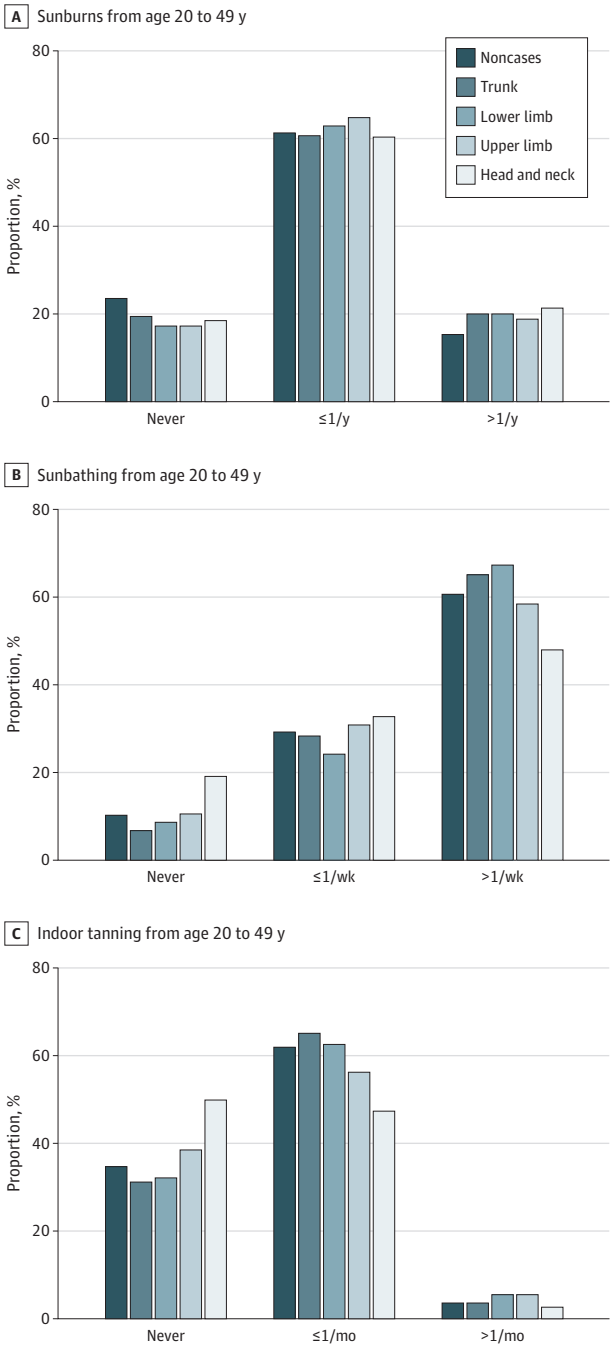
[b] Test for difference by body site.

as fair skin, freckling, red hair, and tanning response to UVR exposure.[34] Melanocortin-1 receptor variants are associated with *BRAF* mutations and melanomas on the trunk and limbs.[34-36] In our study, light skin color, blond and yellow hair, and freckling were associated with increased risk of trunk and limb melanomas but not head and neck melanoma, in line with the molecular findings. Red hair was significantly associated with increased risk of melanoma over all sites, although associations were strongest for the trunk and limbs. In a meta-analysis of 24 epidemiologic studies, light hair color and freckling were more strongly associated with melanoma on the trunk and limbs, and light skin color was more strongly associated with melanomas on the head and arms.[18]

Our finding of a dose-response association between the number of large asymmetric nevi and melanoma in all sites, with a greater dose-response association for trunk and lower limb melanomas compared with upper limb and head and neck melanomas, is consistent with the literature,[13,16,18] as is the significant association found between the number of small nevi with melanoma risk on all sites.[13,18] According to the divergent pathway hypothesis, people with an inherently high propensity for melanocytic proliferation (indicated by a high nevus count) require only a modest level of sun exposure to initiate melanoma on body sites with many nevi,[12] such as the back in men and legs in women.[37] Lack of distinctive heterogeneity of association between the number of nevi and site of melanoma in epidemiologic studies[18] might reflect the complexity of the association between sun exposure, age, number of nevi, and melanoma. The number of nevi reflects both inherent genetic factors and sun exposure[38,39] and is inversely associated with long-term sun exposure and increasing age.[40,41]

The risk of head and neck melanoma was doubled with outdoor work, with no significant association for the other sites, supporting previous reports.[13,15] Conversely, mean lifetime number of sunburns was associated with risk of trunk and limb melanomas but not head and neck melanomas. However, we found no heterogeneity of association between the number of sunburns before age 20 years or sunburns up to age 49 years and melanoma by site, again consistent with previous

Figure. Proportions of Annual Numbers of Sunburns, Weeks of Sunbathing, and Indoor Tanning Sessions in Women Aged 20 to 49 Years



reports,[15,17] and the likelihood that sunburn is a component of both pathways.[17] The number of sunburns has been associated with actinic keratosis[42] and solar elastosis,[13] which are indicators of long-term sun exposure, reflecting the large total doses of UVR that multiple sunburns represent.[13,17] The importance of sunburn before age 20 years was notable in our results.

The heterogeneity of association between history of sunbathing vacations and site-specific melanoma risk is in agreement with the literature and the nevus-associated pathway.[15] However, the heterogeneity of association between upper and lower limb melanomas suggests that the risk profile of lower limb melanomas resembles that of trunk melanomas, arising through the nevus-associated pathway, and the risk profile of upper limb melanomas resembles that of head and neck melanomas. Moreover, our finding that history of sunbathing vacations before age 20 years is associated with increased risk of lower limb melanomas is worth attention in prevention strategies, considering that lower limbs are the most frequent melanoma sites in women. Unexpectedly, a history of sunbathing vacations tended to be inversely associated with risk of head and neck melanoma in our study. A pooled analysis of 13 studies reported no association between intermittent sun exposure and head and neck melanomas.[15] One likely explanation for the apparent inverse association is that intermittent sun exposure might be inversely associated with long-term sun exposure. We found that working outdoors was significantly associated with lower mean weeks of sunbathing vacation; also, women diagnosed with head and neck melanoma reported fewer weeks of sunbathing vacation compared with others. Thus, the lower risk of head and neck melanoma might have been negatively confounded by chronic sun exposure. However, we had no detailed information on chronic sun exposure, and only a subsample of the cohort was asked about outdoor work. Another possible explanation is false protectivity, which can arise with lack of independence among competing outcomes[43,44] (in our study, melanoma in different sites). If an unmeasured factor, such as a genetic or environmental factor, increases the risk of one outcome or initiates it earlier in time, it increases the probability that the individual is censored with respect to the other outcome and can induce a false association.

A previous study reported a dose-response association between indoor tanning and risk of melanoma in this cohort[21]; however, the study lacked power to perform a proper site-specific analysis owing to shorter follow-up time. Our current results suggest that, similar to sunbathing, indoor tanning is associated with melanoma on the trunk and lower limbs. To our knowledge, 2 other studies reported an association between indoor tanning and site-specific risk of melanoma,[45,46] but one study lacked power to estimate for the association with head and neck melanoma and both studies combined upper and lower limb melanomas. Thus, these are novel findings.

Limitations

Several limitations must be noted. Lack of information on site-specific sunburns and site-specific use of sunscreen is a limitation. Moreover, we do not know if melanomas occurred on distal or proximal parts of the limbs. It is suggested that nevus-associated melanomas typically affect proximal limbs that are usually intermittently exposed to the sun, whereas other melanomas affect distal limbs that are usually exposed to the sun long term[32,36]; thus, combining distal and proximal melanomas might dilute a true difference. Our results may not be generalizable to men because their site-specific pattern of sun exposure may differ from that in women. We have tested many

Table 3. Risk of Melanoma Overall and Site-Specific Risk of Melanoma According to UVR Exposure

Characteristic	Total (N = 1310)		Trunk (n = 461)		Lower Limb (n = 520)		Upper Limb (n = 219)		Head and Neck (n = 110)		*P* Value for Heterogeneity[b]
	Cases, No.	RR (95% CI)[a]	Cases, No.	RR (95% CI)[a]	Cases, No.	RR (95% CI)[a]	Cases, No.	RR (95% CI)[a]	Cases, No.	RR (95% CI)[a]	
Residential ambient UVR											
Low (northern Norway)	148	1 [Reference]	49	1 [Reference]	50	1 [Reference]	35	1 [Reference]	14	1 [Reference]	.22
Medium-low (central Norway)	154	1.51 (1.20-1.90)	54	2.15 (1.46-3.17)	59	2.20 (1.50-3.24)	26	1.58 (0.95-2.62)	15	2.62 (1.25-5.47)	
Medium (southwestern Norway)	282	2.06 (1.68-2.52)	92	2.39 (1.68-3.40)	115	2.84 (1.99-4.00)	46	1.81 (1.16-2.82)	29	3.28 (1.72-6.27)	
High (southeastern Norway)	726	1.77 (1.48-2.13)	266	2.45 (1.80-3.35)	296	2.60 (1.92-3.52)	112	1.57 (1.08-2.30)	52	2.15 (1.18-3.94)	
P value for trend	NA	<.001	NA	<.001	NA	<.001	NA	.05	NA	.02	NA
Outdoor work											
No	515	1 [Reference]	192	1 [Reference]	205	1 [Reference]	81	1 [Reference]	37	1 [Reference]	.21
Yes	92	1.25 (1.00-1.56)	27	0.97 (0.65-1.45)	36	1.18 (0.83-1.69)	18	1.53 (0.92-2.56)	11	2.07 (1.06-4.04)	
History of sunburns											
Before age 20 y											
None	163	1 [Reference]	54	1 [Reference]	63	1 [Reference]	31	1 [Reference]	15	1 [Reference]	.80
≤1 per year	292	1.65 (1.39-1.96)	261	1.73 (1.29-2.33)	292	1.62 (1.21-2.14)	118	1.47 (0.98-2.19)	66	1.74 (0.99-1.07)	
>1 per year	125	2.06 (1.69-2.50)	118	2.29 (1.65-3.18)	125	1.97 (1.42-2.73)	54	1.99 (1.26-3.15)	20	1.57 (0.79-3.11)	
P value for trend	NA	<.001	NA	<.001	NA	<.001	NA	.003	NA	.11	NA
Combined age <20 y and 20-49 y											
None, none	81	1 [Reference]	27	1 [Reference]	32	1 [Reference]	15	1 [Reference]	7	1 [Reference]	.88
None, ever	66	0.91 (0.66-1.26)	22	0.89 (0.51-1.56)	24	0.81 (0.48-1.39)	15	1.21 (0.59-2.50)	5	0.92 (0.29-2.92)	
≤1 per year, none	109	1.69 (1.26-2.25)	44	2.00 (1.24-3.24)	40	1.51 (0.95-2.43)	15	1.30 (0.63-2.65)	10	2.02 (0.78-5.27)	
≤1 per year, ever	556	1.58 (1.24-2.01)	193	1.59 (1.06-2.40)	221	1.49 (1.01-2.20)	90	1.51 (0.87-2.63)	52	2.11 (0.94-4.67)	
>1 per year, ever	279	2.00 (1.54-2.59)	100	2.08 (1.34-3.22)	116	1.95 (1.29-2.97)	44	1.86 (1.02-3.40)	19	2.07 (0.86-4.97)	
P value for trend	NA	<.001	NA	<.001	NA	<.001	NA	.04	NA	.01	NA
Mean No. of sunburns per y	1181	1.20 (1.13-1.28)	409	1.21 (1.09-1.33)	466	1.23 (1.11-1.36)	205	1.19 (1.04-1.37)	101	1.09 (0.87-1.37)	.76
History of sunbathing vacation											
Before age 20 y											
None	469	1 [Reference]	161	1 [Reference]	170	1 [Reference]	86	1 [Reference]	52	1 [Reference]	.007
≤1 wk/y	428	1.21 (1.05-1.38)	154	1.20 (0.94-1.52)	166	1.30 (1.03-1.64)	72	1.24 (0.88-1.77)	36	1.01 (0.65-1.57)	
>1 wk/y	275	1.31 (1.12-1.52)	94	1.24 (0.95-1.62)	134	1.72 (1.35-2.18)	35	1.01 (0.66-1.54)	12	0.58 (0.30-1.11)	
P value for trend	NA	<.001	NA	.08	NA	<.001	NA	.73	NA	.14	NA

(continued)

Table 3. Risk of Melanoma Overall and Site-Specific Risk of Melanoma According to UVR Exposure (continued)

Characteristic	Total (N = 1310)		Trunk (n = 461)		Lower Limb (n = 520)		Upper Limb (n = 219)		Head and Neck (n = 110)		*P* Value for Heterogeneity[b]
	Cases, No.	RR (95% CI)[a]	Cases, No.	RR (95% CI)[a]	Cases, No.	RR (95% CI)[a]	Cases, No.	RR (95% CI)[a]	Cases, No.	RR (95% CI)[a]	
Combined age <20 y and 20-49 y											
None, none	89	1 [Reference]	23	1 [Reference]	33	1 [Reference]	18	1 [Reference]	15	1 [Reference]	.002
None, ≤1 wk/y	197	1.04 (0.81-1.35)	70	1.39 (0.86-1.56)	66	0.87 (0.57-1.32)	40	1.25 (0.70-2.21)	21	0.76 (0.38-1.50)	
None, >1 wk/y	177	1.08 (0.83-1.40)	67	1.54 (0.94-2.50)	69	1.05 (0.69-1.60)	26	0.92 (0.49-1.71)	15	0.61 (0.30-1.26)	
≤1 wk/y, ≤1 wk/y	67	0.89 (0.65-1.24)	26	1.28 (0.72-2.28)	20	0.67 (0.38-1.17)	12	0.95 (0.45-2.01)	9	0.85 (0.36-1.99)	
≤1 wk/y, >1 wk/y	343	1.40 (1.10-1.78)	122	1.83 (1.15-2.92)	138	1.43 (0.97-2.12)	59	1.40 (0.81-2.43)	24	0.66 (0.34-1.29)	
>1 wk/y, ever	267	1.38 (1.07-1.77)	90	1.71 (1.06-2.76)	131	1.67 (1.13-2.47)	35	1.09 (0.59-1.99)	11	0.41 (0.18-0.93)	
P value for trend	NA	<.001	NA	.007	NA	<.001	NA	.54	NA	.09	NA
Sunbathing vacation, mean No. of wk/y	1240	1.08 (1.04-1.13)	436	1.14 (1.07-1.22)	493	1.12 (1.05-1.19)	208	0.98 (0.88-1.09)	103	0.87 (0.73-1.04)	.006
History of indoor tanning[c]											
Never	179	1 [Reference]	107	1 [Reference]	131	1 [Reference]	33	1 [Reference]	41	1 [Reference]	.12
Ever	397	1.18 (1.02-1.29)	274	1.21 (0.97-1.52)	326	1.18 (0.96-1.46)	122	0.98 (0.71-1.33)	54	0.72 (0.54-1.06)	
Cumulative No. of indoor tanning sessions											
None	345	1 [Reference]	107	1 [Reference]	131	1 [Reference]	66	1 [Reference]	41	1 [Reference]	.002
Lowest tertile	193	1.12 (0.95-1.29)	67	0.98 (0.75-1.29)	77	0.90 (0.70-1.16)	32	0.54 (0.35-0.81)	17	0.51 (0.29-0.90)	
Middle tertile	146	1.21 (1.01-1.35)	98	1.86 (1.39-2.48)	106	1.74 (1.33-2.28)	41	1.44 (0.97-2.15)	19	0.91 (0.49-1.67)	
Highest tertile	319	1.29 (1.10-1.45)	109	1.33 (1.00-1.76)	143	1.49 (1.16-1.92)	49	1.00 (0.67-1.47)	18	0.70 (0.39-1.26)	
P value for trend	NA	<.001	NA	.005	NA	<.001	NA	.35	NA	.17	NA

Abbreviations: NA, not applicable; RR, relative risk; UVR, UV radiation.

[a] Poison regression analysis adjusted for attained age, birth cohort, skin color, hair color, education, and residential ambient UVR exposure.

[b] Test for difference by body site.

[c] Additionally adjusted for cumulative number of sunburns and cumulative number of weeks on sunbathing vacations.

risk factors for multiple sites; thus, the *P* values must be interpreted bearing this in mind.

Conclusions

This large prospective study appears to provide evidence on divergent pathways to melanoma. Our results suggest similar associations for lower limb and trunk melanomas arising through the nevus-associated pathway, whereas upper limb and head and neck melanomas arise through the long-term sun exposure pathway. Our results suggest that, similar to sunbathing, indoor tanning is associated with trunk and lower limb melanomas. Moreover, our finding that sunbathing vacations before the age of 20 years is associated with significantly increased risk of lower limb melanomas highlights the importance of starting sun protection early in life.

ARTICLE INFORMATION

Accepted for Publication: September 10, 2018.

Published Online: November 21, 2018. doi:10.1001/jamadermatol.2018.3964

Author Affiliations: Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway (Ghiasvand, Rueegg, Veierød); Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway (Robsahm, Weiderpass); Population Health Department, QIMR Berghofer Medical Research Institute, Brisbane, Australia (Green); Cancer Research UK Manchester and Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom (Green); Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway (Weiderpass, Lund); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (Weiderpass); Genetic Epidemiology Group, Folkhälsen Research Center, and Faculty of Medicine, University of Helsinki, Helsinki, Finland (Weiderpass).

Author Contributions: Dr Ghiasvand had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ghiasvand.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Ghiasvand.
Obtained funding: Veierød.
Administrative, technical, or material support: Lund, Veierød.
Supervision: Veierød.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by a grant (project 6823329) from the Norwegian Cancer Society.

Role of the Funder/Sponsor: The Norwegian Cancer Society had no role in the design and conduct of the study; collection, management, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Information: Dr Rueegg has received funding from the European Union Seventh Framework Programme (FP7-PEOPLE-2013-COFUND) under grant agreement 609020-Scientia Fellows, cofunded by the Norwegian Cancer Society (grant 2197685) and the Institute of Basic Medical Sciences, University of Oslo.

REFERENCES

1. Whiteman DC, Green AC, Olsen CM. The growing burden of invasive melanoma: projections of incidence rates and numbers of new cases in six susceptible populations through 2031. *J Invest Dermatol*. 2016;136(6):1161-1171. doi:10.1016/j.jid.2016.01.035

2. Karimkhani C, Green AC, Nijsten T, et al. The global burden of melanoma: results from the Global Burden of Disease Study 2015. *Br J Dermatol*. 2017;177(1):134-140. doi:10.1111/bjd.15510

3. Lucas R, McMichael T, Smith W, Armstrong BK, Prüss-Üstün A. *Solar ultraviolet radiation: global burden of disease from solar ultraviolet radiation. World Health Organization IV Series: environmental burden of disease series; no 13*. Geneva, Switzerland: World Health Organization; 2006.

4. Gandini S, Autier P, Boniol M. Reviews on sun exposure and artificial light and melanoma. *Prog Biophys Mol Biol*. 2011;107(3):362-366. doi:10.1016/j.pbiomolbio.2011.09.011

5. Berwick M, Buller D, Cust A, et al. Melanoma epidemiology and prevention. In: Kaufman HL, Mehnert JM, eds. *Melanoma*. Vol 167. Basel, Switzerland: Springer International Publishing; 2016:17-49. doi:10.1007/978-3-319-22539-5_2

6. Vuong K, Armstrong BK, Weiderpass E, et al; Australian Melanoma Family Study Investigators. Development and external validation of a melanoma risk prediction model based on self-assessed risk factors. *JAMA Dermatol*. 2016;152(8):889-896. doi:10.1001/jamadermatol.2016.0939

7. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma, I: common and atypical naevi. *Eur J Cancer*. 2005;41(1):28-44. doi:10.1016/j.ejca.2004.10.015

8. Bataille V, Snieder H, MacGregor AJ, Sasieni P, Spector TD. Genetics of risk factors for melanoma: an adult twin study of nevi and freckles. *J Natl Cancer Inst*. 2000;92(6):457-463. doi:10.1093/jnci/92.6.457

9. Garbe C, Büttner P, Weiss J, et al. Associated factors in the prevalence of more than 50 common melanocytic nevi, atypical melanocytic nevi, and actinic lentigines: multicenter case-control study of the Central Malignant Melanoma Registry of the German Dermatological Society. *J Invest Dermatol*. 1994;102(5):700-705. doi:10.1111/1523-1747.ep12374298

10. Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst*. 2003;95(11):806-812. doi:10.1093/jnci/95.11.806

11. Green A. A theory of site distribution of melanomas: Queensland, Australia. *Cancer Causes Control*. 1992;3(6):513-516. doi:10.1007/BF00052747

12. Whiteman DC. Testing the divergent pathway hypothesis for melanoma: recent findings and future challenges. *Expert Rev Anticancer Ther*. 2010;10(5):615-618. doi:10.1586/era.10.42

13. Kvaskoff M, Pandeya N, Green AC, et al. Solar elastosis and cutaneous melanoma: a site-specific analysis. *Int J Cancer*. 2015;136(12):2900-2911. doi:10.1002/ijc.29335

14. Kvaskoff M, Pandeya N, Green AC, et al. Site-specific determinants of cutaneous melanoma: a case-case comparison of patients with tumors arising on the head or trunk. *Cancer Epidemiol Biomarkers Prev*. 2013;22(12):2222-2231. doi:10.1158/1055-9965.EPI-13-0475

15. Chang YM, Barrett JH, Bishop DT, et al. Sun exposure and melanoma risk at different latitudes: a pooled analysis of 5700 cases and 7216 controls. *Int J Epidemiol*. 2009;38(3):814-830. doi:10.1093/ije/dyp166

16. Olsen CM, Zens MS, Stukel TA, et al. Nevus density and melanoma risk in women: a pooled analysis to test the divergent pathway hypothesis. *Int J Cancer*. 2009;124(4):937-944. doi:10.1002/ijc.24011

17. Olsen CM, Zens MS, Green AC, et al. Biologic markers of sun exposure and melanoma risk in women: pooled case-control analysis. *Int J Cancer*. 2011;129(3):713-723. doi:10.1002/ijc.25691

18. Caini S, Gandini S, Sera F, et al. Meta-analysis of risk factors for cutaneous melanoma according to anatomical site and clinico-pathological variant. *Eur J Cancer*. 2009;45(17):3054-3063. doi:10.1016/j.ejca.2009.05.009

19. Randi G, Naldi L, Gallus S, Di Landro A, La Vecchia C; Oncology Study Group of the Italian Group for Epidemiologic Research in Dermatology (GISED). Number of nevi at a specific anatomical site and its relation to cutaneous malignant melanoma. *J Invest Dermatol*. 2006;126(9):2106-2110. doi:10.1038/sj.jid.5700334

20. Ghiasvand R, Rueegg CS, Weiderpass E, Green AC, Lund E, Veierød MB. Ghiasvand et al respond to 'indoor tanning—a melanoma accelerator?'. *Am J Epidemiol*. 2017;185(3):160-161.

21. Ghiasvand R, Rueegg CS, Weiderpass E, Green AC, Lund E, Veierød MB. Indoor tanning and melanoma risk: long-term evidence from a prospective population-based cohort study. *Am J Epidemiol*. 2017;185(3):147-156.

22. Colantonio S, Bracken MB, Beecker J. The association of indoor tanning and melanoma in

adults: systematic review and meta-analysis. *J Am Acad Dermatol*. 2014;70(5):847-857. doi:10.1016/j.jaad.2013.11.050

23. El Ghissassi F, Baan R, Straif K, et al; WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens—part D: radiation. *Lancet Oncol*. 2009;10(8):751-752. doi:10.1016/S1470-2045(09)70213-X

24. Lund E, Dumeaux V, Braaten T, et al. Cohort profile: the Norwegian Women and Cancer Study—NOWAC—Kvinner og kreft. *Int J Epidemiol*. 2008;37(1):36-41. doi:10.1093/ije/dym137

25. Veierød MB, Parr CL, Lund E, Hjartåker A. Reproducibility of self-reported melanoma risk factors in a large cohort study of Norwegian women. *Melanoma Res*. 2008;18(1):1-9. doi:10.1097/CMR.0b013e3282f120d2

26. *Cancer in Norway 2016: Cancer Incidence, Mortality, Survival and Prevalence in Norway*. Oslo, Norway: Cancer Registry of Norway; 2017.

27. Ghiasvand R, Lund E, Edvardsen K, Weiderpass E, Veierød MB. Prevalence and trends of sunscreen use and sunburn among Norwegian women. *Br J Dermatol*. 2015;172(2):475-483. doi:10.1111/bjd.13434

28. Ghiasvand R, Weiderpass E, Green AC, Lund E, Veierød MB. Sunscreen use and subsequent melanoma risk: a population-based cohort study. *J Clin Oncol*. 2016;34(33):3976-3983. doi:10.1200/JCO.2016.67.5934

29. Veierød MB, Adami HO, Lund E, Armstrong BK, Weiderpass E. Sun and solarium exposure and melanoma risk: effects of age, pigmentary characteristics, and nevi. *Cancer Epidemiol Biomarkers Prev*. 2010;19(1):111-120. doi:10.1158/1055-9965.EPI-09-0567

30. Veierød MB, Weiderpass E, Thörn M, et al. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. *J Natl Cancer Inst*. 2003;95(20):1530-1538. doi:10.1093/jnci/djg075

31. Wang M, Spiegelman D, Kuchiba A, et al. Statistical methods for studying disease subtype heterogeneity. *Stat Med*. 2016;35(5):782-800. doi:10.1002/sim.6793

32. Whiteman DC, Pavan WJ, Bastian BC. The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. *Pigment Cell Melanoma Res*. 2011;24(5):879-897. doi:10.1111/j.1755-148X.2011.00880.x

33. Pasquali E, García-Borrón JC, Fargnoli MC, et al; M-SKIP Study Group. MC1R variants increased the risk of sporadic cutaneous melanoma in darker-pigmented Caucasians: a pooled-analysis from the M-SKIP project. *Int J Cancer*. 2015;136(3):618-631.

34. Landi MT, Bauer J, Pfeiffer RM, et al. MC1R germline variants confer risk for *BRAF*-mutant melanoma. *Science*. 2006;313(5786):521-522. doi:10.1126/science.1127515

35. Fargnoli MC, Pike K, Pfeiffer RM, et al. MC1R variants increase risk of melanomas harboring BRAF mutations [published correction appears in J *Invest Dermatol*. 2008;128(10):2546]. *J Invest Dermatol*. 2008;128(10):2485-2490. doi:10.1038/jid.2008.67

36. Shain AH, Bastian BC. From melanocytes to melanomas. *Nat Rev Cancer*. 2016;16(6):345-358. doi:10.1038/nrc.2016.37

37. Nicholls EM. Development and elimination of pigmented moles, and the anatomical distribution of primary malignant melanoma. *Cancer*. 1973;32(1):191-195. doi:10.1002/1097-0142(197307)32:1<191::AID-CNCR2820320129>3.0.CO;2-W

38. Wachsmuth RC, Gaut RM, Barrett JH, et al. Heritability and gene-environment interactions for melanocytic nevus density examined in a UK adolescent twin study. *J Invest Dermatol*. 2001;117(2):348-352. doi:10.1046/j.0022-202x.2001.01415.x

39. Wachsmuth RC, Turner F, Barrett JH, et al. The effect of sun exposure in determining nevus density in UK adolescent twins. *J Invest Dermatol*. 2005;124(1):56-62. doi:10.1111/j.0022-202X.2004.23548.x

40. Harth Y, Friedman-Birnbaum R, Linn S. Influence of cumulative sun exposure on the prevalence of common acquired nevi. *J Am Acad Dermatol*. 1992;27(1):21-24. doi:10.1016/0190-9622(92)70149-A

41. Armstrong BK, Cust AE. Sun exposure and skin cancer, and the puzzle of cutaneous melanoma: a perspective on Fears et al: mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States: *American Journal of Epidemiology* 1977;105:420-427. *Cancer Epidemiol*. 2017;48:147-156. doi:10.1016/j.canep.2017.04.004

42. Kennedy C, Bajdik CD, Willemze R, De Gruijl FR, Bouwes Bavinck JN; Leiden Skin Cancer Study. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. *J Invest Dermatol*. 2003;120(6):1087-1093. doi:10.1046/j.1523-1747.2003.12246.x

43. Di Serio C. The protective impact of a covariate on competing failures with an example from a bone marrow transplantation study. *Lifetime Data Anal*. 1997;3(2):99-122. doi:10.1023/A:1009672300875

44. Stensrud MJ, Valberg M, Røysland K, Aalen OO. Exploring selection bias by causal frailty models: the magnitude matters. *Epidemiology*. 2017;28(3):379-386. doi:10.1097/EDE.0000000000000621

45. Nielsen K, Måsbäck A, Olsson H, Ingvar C. A prospective, population-based study of 40,000 women regarding host factors, UV exposure and sunbed use in relation to risk and anatomic site of cutaneous melanoma. *Int J Cancer*. 2012;131(3):706-715. doi:10.1002/ijc.26408

46. Cust AE, Armstrong BK, Goumas C, et al. Sunbed use during adolescence and early adulthood is associated with increased risk of early-onset melanoma. *Int J Cancer*. 2011;128(10):2425-2435. doi:10.1002/ijc.25576