ORIGINAL REPORT

Nevus Count, Pigmentary Characteristics, and Melanoma-specific Mortality among Norwegian Women with Melanoma >1.0 mm Thick

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Little is known about if and how nevi and pigmentation are associated with melanoma-specific mortality. However, increased melanoma awareness in people with lighter pigmentation and many nevi may result in earlier diagnosis of thinner less-lethal tumors. The aim of this study was to investigate associations between nevus count (asymmetrical >5 mm and small symmetrical), pigmentary characteristics (hair colour, eye colour, skin colour, freckling, pigmentary score), and melanoma-specific mortality in subjects with melanomas >1 mm. Data from the Norwegian Women and Cancer cohort, established in 1991, with complete follow-up of melanoma patients until 2018 through the Cancer Registry of Norway, were used to estimate hazard ratios with 95% confidence intervals for the associations between nevus count, pigmentary characteristics, and melanoma-specific mortality, stratified by tumor thickness using Cox regression. Estimated hazard ratios consistently indicated a higher risk of melanoma death for those with darker vs lighter pigmentary characteristics in patients with tumors >1.0–2.0 mm and >2.0 mm thick (e.g. pigmentary score hazard ratio 1.25, 95% confidence interval (0.74–2.13)). Among women with melanomas >1.0 mm thick, lighter pigmentation and asymmetrical nevi may be associated with lower melanoma-specific mortality, suggesting that factors that increase the risk of melanoma may also be associated with decreased risk of death from melanoma.

Key words: awareness; epidemiology; neoplasms; nevus; melanoma; mortality; pigmentation.

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SIGNIFICANCE

Naevi, fair complexion, and a tendency to sunburn are well-known risk factors for melanoma, but have been less studied as prognostic factors. This population-based cohort study among women with primary invasive melanomas >1.0 mm thick suggests a higher risk of melanoma death among women with darker vs lighter hair, eye and skin colour, higher pigmentary score, and milder skin reaction to acute sun exposure. The results also indicate an interaction effect, with poorer survival in darker individuals with asymmetrical nevi >5 mm. More research is needed to understand the differential diagnostic outcomes among those with and without traditional melanoma risk factors.

Naevi, fair complexion, and inability to tan are well-known host risk factors for melanoma (1). However, less is known about whether nevi and pigmentation are associated with melanoma prognosis and, if so, the mechanisms that might drive these associations. Given that both nevi and pigmentation are genetically determined (1, 2), highly correlated (3), and strong risk factors for melanoma, some studies propose that there may be biological associations between nevi, pigmentation, and melanoma mortality (4, 5). However, the results are limited and mixed. Three studies have found associations between high nevus count and lower melanoma-specific mortality (6–8). However, others have found associations between high nevus count and poor melanoma prognosis (9), particularly in men (10). Similarly, with pigmentation, some studies have suggested associations in both directions with prognostic factors (11, 12), while others have suggested no association with melanoma-specific mortality (13, 14).

The association between nevi, pigmentation, and melanoma-specific mortality may be confounded by awareness and screening. Skin self-examination (SSE) and melanoma awareness may be associated with lower melanoma-specific mortality (15, 16). Given that SSE is often recommended for people with many nevi, increased awareness may result in an earlier stage at diagnosis (17) and improved survival. Similarly, both freckling and red/blonde hair colour and, by association, poor tanning ability (1), are associated with increased melanoma awareness in women (18), which may affect survival outcomes.

Higher levels of education are also associated with both SSE (19) and lower melanoma-specific mortality (20). However, the extent to which this increased awareness and screening affect melanoma-specific mortality is unclear, with some studies reporting no associations (21).

Current findings regarding associations between nevi, pigmentary characteristics, and melanoma prognosis come primarily from studies in case subjects from case-control studies (13–15), or studies focusing on associations with well-established prognostic factors (11, 22, 23) rather than melanoma-specific mortality. In addition, few studies have differentiated between the role of common nevi and atypical nevi in melanoma-specific mortality. Given that melanoma awareness may improve melanoma outcomes through the diagnosis of thinner tumors, and that there is a low rate of survival in patients with melanoma diagnosed with tumours > 1.0 mm, the focus should be on factors that affect melanoma-specific mortality among those diagnosed with tumurs > 1.0 mm, in order to reduce the possible influence of non-biological factors.

The aim of this study was to investigate associations between common and atypical nevus counts, pigmentary characteristics, and melanoma-specific mortality among women diagnosed with melanoma > 1.0 mm, using data from the Norwegian Women and Cancer (NOWAC) study, a prospective population-based cohort containing detailed information on individual host and lifestyle factors.

MATERIALS AND METHODS

The NOWAC cohort

NOWAC was established in 1991. Between 1991 and 2007 over 300,000 women aged 30–75 years, randomly selected from the Norwegian National Population register, were sent invitation letters (24). More than 172,000 women (response 54%) answered the baseline questionnaire. Participants received follow-up questionnaires every 4–6 years (80% response first follow-up, 79% response second follow-up). Details of NOWAC are published elsewhere (24). Unique personal identification numbers of Norwegian citizens link NOWAC to the Cancer Registry of Norway (CRN), the Norwegian Melanoma Registry (NMR), and the Norwegian Cause of Death Registry. This linkage provides complete and high-quality data on cancer diagnoses and death (25) until 31 December 2018.

All participants provided written informed consent, and data handling followed relevant ethics guidelines and regulations. The study was approved by the Regional Committees for Medical and Health Research Ethics of Northern Norway (2021/252094/REK Nord) and the Norwegian Center for Research Data (2021/147992).

Pigmentary characteristics

Participants reported hair colour, eye colour, untanned skin colour (using a 1×9-cm colour scale graded from 1 (very fair) to 10 (dark brown)), and whether they freckled when sunbathing. Skin colour was categorized as very dark (grades 9–10), darker (grades 6–8), medium (grades 4–5), or light (grades 1–3). A combined pigmentary score was constructed by summing values of skin colour (darker = 0, medium = 1, light = 2), eye colour (brown = 0, grey/green/mixed = 1, blue = 2), hair colour (dark brown/black = 0, brown = 1, blonde/yellow = 2, red = 3), and freckling (no = 0, yes = 1) and categorized as darker (score < 3), medium (scores 3–5) and fair (scores 6–8) (11). Participants reported number of asymmetrical nevi > 5 mm on their arms (armpit to fingers) or legs (groin to toes) (categorized as 0, 1, ≥ 2, and 0, ≥ 1, respectively). A colour brochure with pictures showing examples of asymmetrical nevi was provided to increase self-reported accuracy. A subsample of women reported their skin's reaction to acute (brown, red, red with pain, red with pain and blisters) and chronic (deep brown, brown, light brown, never brown) sun exposure, and the number of small symmetrical nevi on their arms or legs (categorized as 0, 1–10, 11–50, ≥ 51 and ≤ 10, > 10). Over the course of NOWAC, the questionnaire has been modified, and thus not all women were asked all questions regarding pigmentation and nevi. Reproducibility has been studied for freckling when sunbathing (kappa = 0.77), small symmetrical nevi on arms (weighted kappa = 0.65), and the skin colour scale (interclass correlation coefficient = 0.59) (26).

Histopathological melanoma variables

Data on melanoma diagnoses were categorized according to the International Classification of Diseases, 7th Revision (27): head/neck (190.0), trunk (190.1/190.7), upper limbs (190.2), lower limbs (190.3/190.4), other (190.5/190.6/190.8), and skin not otherwise specified (190.9). Histological subtype of each tumor was categorized as superficial spreading melanoma (SSM; 8743), nodular melanoma (NM; 8721), lentigo maligna melanoma (LMM; 8742), other (8000; 8722; 8730; 8740; 8744; 8745; 8770; 8772), and melanoma unspecified (8720), according to the International Classification of Diseases, 3rd Edition (28). In 2008 the CRN established the NMR, which provided data on tumor thickness. For melanoma cases before 2008, tumor thickness was extracted manually from histopathological reports by experienced registrars at the CRN. The 8th Edition of the American Joint Committee on Cancer (29) was used to categorize melanoma thickness: T1: ≤ 1.0 mm, T2: > 1.0–2.0 mm, T3: > 2.0–4.0 mm, and T4: > 4.0 mm, or unknown if tumor thickness was not recorded. The CRN provided information on clinical stage at diagnosis: local disease (no metastases), regional metastasis (metastases in regional lymph nodes, satellites, and in-transit metastases), and distant metastasis (organ metastases and non-regional lymph node metastases). Data on sentinel lymph node involvement and ulceration status were not available.

Other variables

Region of residence at baseline was categorized as: northern Norway, central Norway, southwestern Norway, and southeastern Norway. Participants also recorded their years of education (≤ 10, 11–13, or ≥ 14 years) at baseline.

Study sample

Of the 172,472 women who completed and returned the questionnaire, 2,728 were diagnosed with a primary invasive melanoma. Exclusion criteria were: women with very dark skin ($n = 1$), those diagnosed with melanoma before study inclusion ($n = 824$), and non-histologically verified diagnoses ($n = 1$). The remaining 1,902 women answered at least 1 question about hair colour, eye colour, skin colour, freckles, or nevi.

Previous findings in NOWAC suggest that fair pigmentation is associated with thinner melanomas, citing increased melanoma awareness (11). To account for awareness, measured by earlier diagnosis and thinner tumors, the analyses were performed based on women diagnosed with melanoma > 1 mm measured thickness, and these were stratified by tumor thickness: intermediate thickness (> 1.0–2.0 mm) and "thick" (> 2.0 mm).

Statistical analysis

Person-years of follow-up were calculated from date of diagnosis to death, emigration, or end of follow-up, whichever came first. Death from melanoma was the primary endpoint, and deaths from other causes were treated as censored observations. Cox proportional hazards regression, stratified by birth cohort, and with time since diagnosis as the time scale, was used to estimate cause-specific hazard ratios (HRs) and confidence intervals (CIs). The proportional hazards assumption was checked using Schoenfeld residuals. Adjustments were determined based on assumptions illustrated in a directed acyclic graph (**Fig. 1**). Since none of the covariates recorded in NOWAC can cause pigmentation, there were no observed confounders for pigmentation. Adjustment for pigmentation was necessary (Fig. 1) for nevi variables; the study adjusted for hair colour as it has been consistently found to be the strongest pigmentary characteristic associated with melanoma in NOWAC and can be representative of sensitivity to ultraviolet (UV) radiation (30). As the study conditioned on a melanoma diagnosis, it also adjusted for variables believed to affect both melanoma diagnosis and death (Z in Fig. 1). Three models were created: model 0: univariable; model 1: model 0 plus age at diagnosis, education, and region of residence. As both pigmentation and nevus count may be associated with prognostic tumor characteristics (11, 22, 23), relationships might be partly explained by associations with tumor characteristics. Thus, we created model 2, which is model 1 plus tumor characteristics (anatomical site, histological subtype, and clinical stage). As the study included few participants with darker features, the fairest features were used as the reference for all variables, except for nevi variables where the lowest numerical category was used as the reference. Supplemental analyses using the models above were also performed in participants with tumors <1.0 mm as well as using all-cause mortality and other cause mortality as endpoints.

Given that NMs account for a large proportion of thick tumors and a majority of melanoma deaths (excluding unspecified melanoma type), analyses were also conducted stratified by subtype on tumors >1 mm (collapsing thick and thicker tumors). In addition, as prevalence of nevi differs by pigmentation (3), stratified analyses were conducted by number of asymmetrical nevi >5 mm on tumors >1 mm (collapsing thick and thicker tumors). Interactions between pigmentation variables and asymmetrical nevi >5 mm were tested using a likelihood ratio test. Categories were collapsed in some variables to improve asymptotic approximations in the analysis. Sensitivity analyses including only women with localized melanoma did not change the results (results not shown). In addition to complete-case analyses, missing values, ranging from 5% to 24%, among nevi variables, pigmentary variables, tumor thickness, and education were imputed using multiple imputation with chained equations with 40 imputed datasets using additional patient demographics and available histopathological melanoma variables. Given that tumor thickness is a good predictor of clinical stage, likelihood of metastasis increases with increasing tumor thickness (31), 32 participants with missing tumor thickness and regional or distant metastasis were classified as having thick tumors (>2 mm) before multiple imputation.

Statistical analysis was performed using the R programming language and software environment (R version 4.0.4 (2021-02-15); The R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-sided with a 5% significance level.

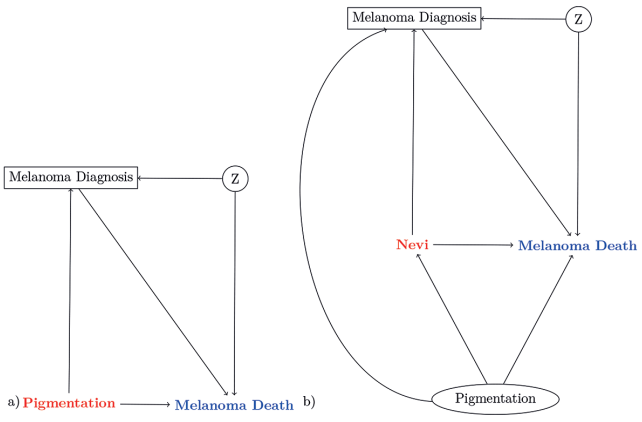

Fig. 1. Directed acyclic graphs (DAGs) showing possible causal pathways between (a) pigmentation and (b) nevi (exposures of interest), other risk factors, and melanoma death (outcome). All nodes represent current covariate levels. Melanoma diagnosis includes all histopathological variables related to melanoma diagnosis, including Breslow thickness, histological subtype, anatomical site, ulceration (unmeasured), sentinel lymph node status (unmeasured), and clinical stage. Z represents other covariates that are related to both melanoma diagnosis and death from melanoma including region of residence, education, and age at diagnosis, and Breslow thickness if used as a proxy for early diagnosis and awareness. By design, the current study conditions on having melanoma, which opens the pathway from the exposure to melanoma death through Z. In order to account for this open pathway, we condition on the known, measured, Z variables. In the case of nevi, pigmentation is a confounding variable, and thus the study must also adjust for pigmentation. Thus, for pigmentation, the minimal sufficient set to get the total effect on melanoma death among those diagnosed with melanoma would be the variables contained in Z (model 1). Similarly, for nevi the study would adjust for the Z variables and pigmentation. Treatment is not related to pigmentation or nevi in Norway and is not included in this DAG as the study is evaluating the total effect. Melanoma diagnosis and stage form the basis for treatment, and thus treatment would be a mediator on the pathway from melanoma diagnosis to melanoma death.

RESULTS

During a mean follow-up of 7.6 (<1–27.5) years, 15.1% (n=288) of the 1,902 women died, including 8.4% (n=159) due to melanoma. The women were in the age range 33.7–91.3 years at diagnosis (mean 62.4 years). Those with thick tumors tended to be older at diagnosis, had a shorter follow-up, and had the highest proportion of deaths due to melanoma (**Table I**). Those with thick tumors were proportionally the least educated. Those with thin (≤1 mm) tumors had marginally fairer pigmentation and fewer asymmetrical nevi >5 mm. Those with tumors >2 mm had more head and neck tumors compared with those with thinner tumors. SSMs made up the largest proportion of tumors <2 mm, while thick tumors were predominantly NM. Finally, proportions of regional and distant metastasis increased with tumor thickness.

Results from multiple imputation analyses were compatible with complete-case analysis (Table SI). This study presents results from the multiple imputation analyses based on the multivariable model (model 1). Complete-case analyses are presented in Tables SIII and SIV. No statistically significant associations were found between melanoma-specific mortality and hair, eye, and skin colour, freckling when sunbathing, pigmentary score, asymmetrical nevi >5 mm, small symmetrical nevi, and chronic sun exposure. However, the estimates for hair, eye and skin colour, and pigmentary score indicate a trend towards a higher risk of melanoma death for those

Table I. Characteristics of the 1,902 incident histologically verified first primary invasive melanoma cases in the Norwegian Women and Cancer cohort (1991 to 2018) stratified by tumor thickness

	Thin (≤1.0 mm) (*n* = 1,103)	Intermediate thickness (>1.0–2.0 mm) (*n* = 371)	Thick (>2.0 mm) (*n* = 281)	Missing (*n* = 147)	Overall (*n* = 1,902)
Age at diagnosis, years, mean (SD)	62 (8.88)	62.5 (9.02)	64.7 (10.2)	60.5 (9.63)	62.4 (9.23)
Age cohort at diagnosis					
<50 years, *n* (%)	89 (8.1)	31 (8.4)	17 (6.0)	17 (11.6)	154 (8.1)
50–59 years, *n* (%)	284 (25.7)	93 (25.1)	55 (19.6)	46 (31.3)	478 (25.1)
60–69 years, *n* (%)	506 (45.9)	157 (42.3)	127 (45.2)	53 (36.1)	843 (44.3)
≥ 70 years, *n* (%)	224 (20.3)	90 (24.3)	82 (29.2)	31(21.1)	427 (22.5)
Person-years of follow-up, mean (SD)	7.91 (6.35)	7.26 (6.17)	6.27 (5.70)	8.04 (7.26)	7.55 (6.32)
Vital status, *n* (%)					
Alive	1,021 (92.6)	307 (82.7)	189 (67.3)	93 (63.3)	1610 (84.6)
Other death	59 (5.3)	24 (6.5)	33 (11.7)	13 (8.8)	129 (6.8)
Melanoma death	20 (1.8)	390 (10.5)	59 (21.0)	41 (27.9)	159 (8.4)
Emigrated	3 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	4 (0.2)
Birth cohort, *n* (%)					
1927–1943	201 (18.2)	67 (18.1)	85 (30.2)	38 (25.9)	391 (20.6)
1944–1948	348 (31.6)	128 (34.5)	79 (28.1)	42 (28.6)	597 (31.4)
1949–1953	306 (27.7)	103 (27.8)	74 (26.3)	38 (25.9)	521 (27.4)
1953–1965	248 (22.5)	73 (19.7)	43 (15.3)	29 (19.7)	393 (20.7)
Region of residence, *n* (%)					
South-eastern Norway	584 (52.9)	215 (58.0)	163 (58.0)	87 (59.2)	1049 (55.2)
South-western Norway	247 (22.4)	73 (19.7)	56 (19.9)	26 (17.7)	402 (21.1)
Central Norway	126 (11.4)	44 (11.9)	28 (10.0)	14 (9.5)	212 (11.1)
Northern Norway	146 (13.2)	39 (10.5)	34 (12.1)	20 (13.6)	239 (12.6)
Education, *n* (%)					
≥14 years	379 (34.4)	128 (34.5)	75 (26.7)	51 (34.7)	633 (33.3)
11–13 years	347 (31.5)	117 (31.5)	82 (29.2)	40 (27.2)	586 (30.8)
≤10 years	325 (29.5)	106 (28.6)	102 (36.3)	53 (36.1)	586 (30.8)
Missing	52 (4.7)	20 (5.4)	22 (7.8)	3 (2.0)	97 (5.1)
Hair colour, *n* (%)					
Blonde/yellow	513 (46.5)	151 (40.7)	142 (50.5)	70 (47.6)	876 (46.1)
Red	84 (7.6)	36 (9.7)	19 (6.8)	5 (3.4)	144 (7.6)
Brown	331 (30.0)	114 (30.7)	69 (24.6)	48 (32.7)	562 (29.5)
Black/dark brown	107 (9.7)	44 (11.9)	32 (11.4)	16 (10.9)	199 (10.5)
Missing	68 (6.2)	26 (7.0)	19 (6.8)	8 (5.4)	121 (6.4)
Eye colour, *n* (%)					
Blue	547 (49.6)	174 (46.9)	137 (48.8)	72 (49.0)	930 (48.9)
Grey/green/mixed	385 (34.9)	140 (37.7)	96 (34.2)	54 (36.7)	675 (35.5)
Brown	101 (9.2)	30 (8.1)	25 (8.9)	13 (8.8)	169 (8.9)
Missing	70 (6.3)	27 (7.3)	23 (8.2)	8 (5.4)	128 (6.7)
Untanned skin colour, *n* (%)					
Lightest	419 (38.0)	137 (36.9)	98 (34.9)	54 (36.7)	708 (37.2)
Medium	333 (30.2)	116 (31.3)	73 (26.0)	45 (30.6)	567 (29.8)
Darker	158 (14.3)	50 (13.5)	38 (13.5)	17 (11.6)	263 (13.8)
Missing	193 (17.5)	6 (18.3)	72 (25.6)	31 (21.1)	364 (19.1)
Freckles when sunbathing, *n* (%)					
Yes	423 (38.4)	139 (37.5)	98 (34.9)	64 (43.5)	724 (38.1)
No	505 (45.8)	169 (45.6)	130 (46.3)	56 (38.1)	860 (45.2)
Missing	175 (15.9)	63 (17.0)	53 (18.9)	27 (18.4)	318 (16.7)
Pigmentary score, *n* (%)					
Fairest	281 (25.5)	88 (23.7)	64 (22.8)	41 (27.9)	474 (24.9)
Medium	479 (43.4)	154 (41.5)	103 (36.7)	57 (38.8)	793 (41.7)
Darker	77 (7.0)	34 (9.2)	23 (8.2)	9 (6.1)	143 (7.5)
Missing	266 (24.1)	95 (25.6)	91 (32.4)	40 (27.2)	492 (25.9)
Asymmetrical nevi >5 mm on arms/legs, *n* (%)					
0	730 (66.2)	240 (64.7)	181 (64.4)	110 (74.8)	1261 (66.3)
1	137 (12.4)	31 (8.4)	29 (10.3)	5 (3.4)	202 (10.6)
≥2	126 (11.4)	57 (15.4)	38 (13.5)	22 (15.0)	243 (12.8)
Missing	110 (10.0)	43 (11.6)	33 (11.7)	10 (6.8)	196 (10.3)
Body site, *n* (%)					
Trunk	398 (36.1)	120 (32.3)	98 (34.9)	34 (23.1)	650 (34.2)
Head/neck	83 (7.5)	26 (7.0)	35 (12.5)	15 (10.2)	159 (8.4)
Upper limb	192 (17.4)	68 (18.3)	46 (16.4)	10 (6.8)	316 (16.6)
Lower limb	410 (37.2)	152 (41.0)	100 (35.6)	36 (24.5)	698 (36.7)
Other	20 (1.8)	5 (1.3)	2 (0.7)	52 (35.4)	79 (4.2)
Subtype, *n* (%)					
Superficial spreading melanoma	845 (76.6)	205 (55.3)	67 (23.8)	40 (27.2)	1157 (60.8)
Nodular melanoma	36 (3.3)	89 (24.0)	137 (48.8)	6 (4.1)	268 (14.1)
Lentigo maligna melanoma	43 (3.9)	5 (1.3)	5 (1.8)	4 (2.7)	57 (3.0)
Unspecified	170 (15.4)	70 (18.9)	59 (21.0)	91 (61.9)	390 (20.5)
Other[b]	9 (0.8)	2 (0.5)	13 (4.6)	6 (4.1)	30 (1.6)
Breslow thickness, mean (IQR)	0.610 (0.40–0.80)	1.50 (1.20–1.80)	4.45 (2.50–4.50)	NA (NA)	1.41 (0.50–1.50)
Clinical stage, *n* (%)					
Local	951 (86.2)	305 (82.2)	204 (72.6)	65 (44.2)	1,525 (80.2)
Regional	6 (0.5)	16 (4.3)	34 (12.1)	7 (4.8)	63 (3.3)
Distant	1 (0.1)	1 (0.3)	8 (2.8)	25 (17.0)	35 (1.8)
Unknown	145 (13.1)	49 (13.2)	35 (12.5)	50 (34.0)	279 (14.7)
Skin reaction to acute sun exposure[a], *n* (%)					
Red with burning and blistering	190 (17.2)	61 (16.4)	44 (15.7)	26 (17.7)	321 (16.9)
Red	372 (33.7)	137 (36.9)	118 (42.0)	63 (42.9)	690 (36.3)
Brown without first being red	109 (9.9)	38 (10.2)	33 (11.7)	1 (10.2)	195 (10.3)
Missing	432 (39.2)	135 (36.4)	86 (30.6)	43 (29.3)	696 (36.6)
Skin reaction to chronic sun exposure[a], *n* (%)					
Light brown/never brown	235 (21.3)	77 (20.8)	77 (27.4)	35 (23.8)	424 (22.3)
Brown	335 (30.4)	123 (33.2)	92 (32.7)	53 (36.1)	603 (31.7)
Deep brown	56 (5.1)	19 (5.1)	15 (5.3)	13 (8.8)	103 (5.4)
Missing	477 (43.2)	152 (41.0)	97 (34.5)	46 (31.3)	772 (40.6)
Small symmetrical nevi on arms/legs[a], *n* (%)					
0	55 (5.0)	16 (4.3)	13 (4.6)	9 (6.1)	93 (4.9)
1–10	159 (14.4)	65 (17.5)	50 (17.8)	21 (14.3)	295 (15.5)
11–50	227 (20.6)	66 (17.8)	55 (19.6)	33 (22.4)	381 (20.0)
≥ 51	116 (10.5)	47 (12.7)	38 (13.5)	19 (12.9)	220 (11.6)
Missing	546 (49.5)	177 (47.7)	125 (44.5)	65 (44.2)	913 (48.0)

[a]Recorded for subsamples of the cohort. [b]Other includes: 8000: neoplasm, malignant; 8722: balloon cell melanoma; 8730: amelanotic melanoma; 8740: malignant melanoma in junctional nevus; 8744: acral lentiginous melanoma, malignant; 8745: desmoplastic melanoma, malignant; 8770: mixed epithelioid and spindle cell melanoma; and 8772: spindle cell nevus, not otherwise specified.
IQR: interquartile range, SD: standard deviation.

with darker vs lighter pigmentation traits among both those with intermediate and thick melanomas (**Fig. 2**). Skin reaction to acute sun exposure was significantly associated with melanoma death among patients with thick melanomas in the complete-case analysis (HRs (95% CIs): 2.59 (1.37–4.89) for brown vs red) (Table SI), but not after multiple imputation (1.54 (0.83–2.88)) (Fig. 2). Estimates among patients with thin tumors (presented for completeness in Table SII) were in the same direction as those with tumors >1 mm. Additional adjustment for tumor-related variables (model 2) did not change the results (Table SV). When repeated using all-cause mortality and other cause mortality as endpoints, results from all-cause mortality were similar to that of melanoma-specific mortality and no statistical or clinically significant associations were observed for other-cause mortality (results not shown).

For both SSM and NM tumors >1 mm, the estimated HRs for hair, eye and skin colour, pigmentary score, and skin reaction to acute sun exposure were also >1 for darker vs lighter pigmentation, though none were significant (**Fig. 3**). For chronic sun exposure, the estimated HRs (95% CIs) were in the opposite direction for SSM (0.54 (0.22–1.26)) and NM (1.39, (0.63–3.05)). HRs below 1 were observed for ≥1 vs 0 asymmetrical nevi >5 mm 1 (0.72 (0.29–1.78)), and for >10 vs ≤10 small symmetrical nevi (0.70 (0.26–1.91)) in SSM, but not NM (Fig. 3). Finally, the estimates suggest stronger associations between pigmentation and melanoma death among those with ≥1 asymmetrical nevi compared with those with no asymmetrical nevi ($0.056 < p_{interaction} < 0.588$; women with tumors >1 mm) (**Table II**). Most notably, darker pigmentation was associated with a higher risk of melanoma-specific death among those with ≥1 asymmetrical nevi >5 mm (1.96 (0.75–5.13)), but not in those without asymmetrical nevi >5 mm (0.97 (0.60–1.56)) ($p_{interaction} = 0.056$).

DISCUSSION

In this population-based cohort, among women diagnosed with primary invasive melanomas >1 mm, estimates trend towards a higher risk of melanoma death among women with darker vs lighter hair, eye and skin colour, higher pigmentary score, and milder skin reaction to acute sun exposure, and reduced risk among women with nevi (small symmetrical and asymmetrical >5 mm) compared with no nevi. Associations between pigmentation and melanoma death were similar for SSM and NM, though differences were seen among nevi variables and skin response to chronic sun exposure. Finally, the results suggest an interaction between pigmentary score and asymmetrical nevi >5 mm, indicating poorer survival in darker individuals with many nevi.

The results of the current study indicate less mortality among women with nevi, which is in agreement with earlier studies (6–8) but in contrast to others (9, 10). With

Levels	Variable	Intermediate thickness (>1.0–2.0 mm)[c] HR (95% CI)[a]	Thick (>2.0 mm)[f] HR (95% CI)[a]
Hair color	Red	0.85 (0.42–1.73)	0.98 (0.33–2.91)
	Blonde/yellow	1	1
	Brown	1.08 (0.74–1.57)	1.26 (0.73–2.18)
	Black/dark brown	1.23 (0.76–1.99)	1.20 (0.62–2.33)
Eye color	Blue	1	1
	Grey/green/mixed	1.29 (0.66–2.51)	1.33 (0.80–2.21)
	Brown	1.10 (0.38–3.17)	1.98 (0.99–3.96)
Skin color	Light	1	1
	Medium	0.65 (0.29–1.47)	1.75 (1.01–3.06)
	Darker	1.18 (0.51–2.72)	1.11 (0.49–2.51)
Freckling when sunbathing	Yes	1	1
	No	1.06 (0.53–2.12)	1.02 (0.62–1.67)
Pigmentary score	Fair	1	1
	Medium/darker	1.12 (0.54–2.33)	1.25 (0.74–2.13)
Skin reaction to acute sun exposure[c]	Red[d]	1	1
	Brown	1.49 (0.68–3.26)	1.54 (0.83–2.88)
Skin reaction to chronic sun exposure[c]	Light brown/never brown	1	1
	Brown/deep brown	0.88 (0.40–1.94)	0.91 (0.55–1.49)
Asymmetrical nevi >5 mm on arms/legs	0	1	1
	≥1	0.74 (0.34–1.59)	0.79 (0.45–1.38)
Small symmetrical nevi on arms/legs[c]	≤10	1	1
	>10	0.80 (0.35–1.81)[b]	0.80 (0.46–1.40)[b]

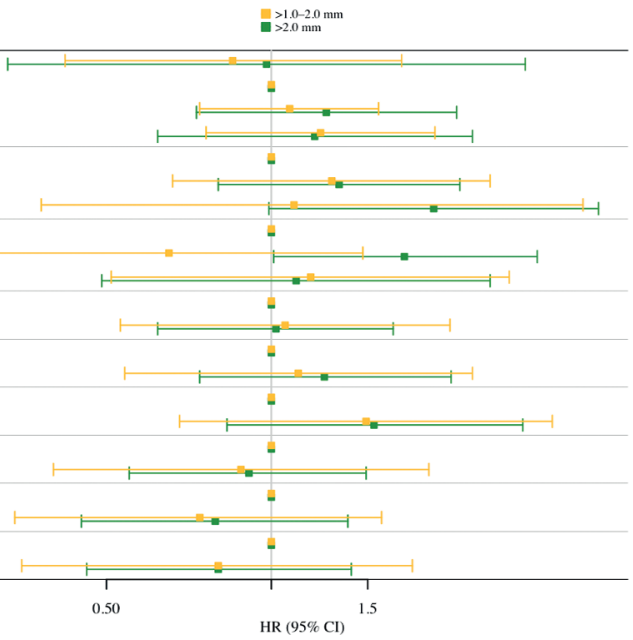

Fig. 2. Hazard ratios (HRs) with 95 confidence intervals (95% CIs) for melanoma-specific death in incident melanoma cases in the Norwegian Women and Cancer cohort (1991 to 2018) by tumor thickness in women with tumors >1 mm. [a]Cox proportional hazards regression stratified by birth cohort, and with time since diagnosis as time scale adjusting for age at diagnosis, region of residence, and education. [b]Cox proportional hazards regression stratified by birth cohort, and with time since diagnosis as time scale adjusting for age at diagnosis, region of residence, education, and hair colour. [c]Recorded for subsamples of the cohort. [d]Red with burning and blistering, and red. [e]Analysis with multiple imputation of missing data conducted using chained equations and a total of 40 imputed data sets, with the same adjustments as the multivariable model (mean $n = 399$, range: 390–410; mean 48 deaths, range: 42–53). [f]Analysis with multiple imputation of missing data conducted using chained equations and a total of 40 imputed data sets, with the same adjustments as the multivariable model (mean $n = 333$, range: 327–340; mean 85 deaths, range: 79–91).

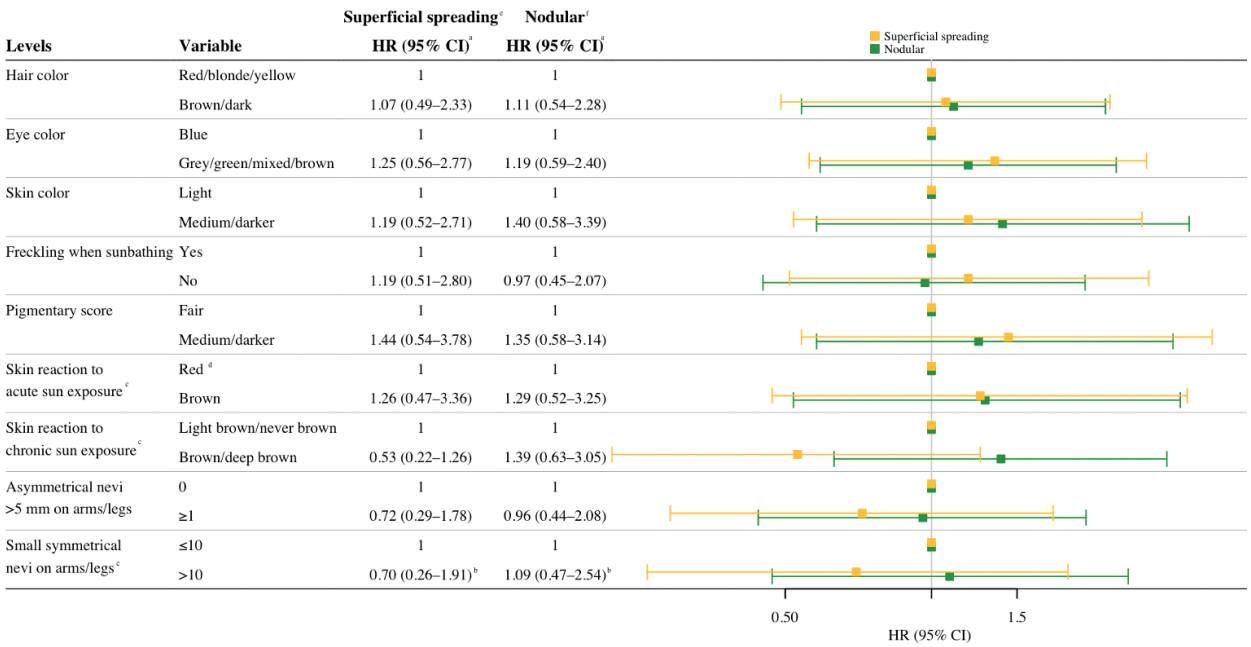

Fig. 3. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) for melanoma-specific death in incident melanoma cases in the Norwegian Women and Cancer cohort (1991 to 2018) by subtype in women with tumors >1 mm. [a]Cox proportional hazards regression stratified by birth cohort, and with time since diagnosis as time scale adjusting for age at diagnosis, region of residence, and education. [b]Cox proportional hazards regression stratified by birth cohort, and with time since diagnosis as time scale adjusting for age at diagnosis, region of residence, education, and hair colour. [c]Recorded for subsamples of the cohort. [d]Red with burning and blistering, and red. Analysis with multiple imputation of missing data conducted using chained equations and a total of 40 imputed data sets, with the same adjustments as the multivariable model: [e]mean $n = 282$, range: 277–287; mean 33 deaths, range: 32–33) and [f]mean $n = 231$, range: 230–232; mean 37 deaths, range: 35–37).

regards to pigmentation, given the lack of statistical significance, the current results are technically in agreement with previous null findings, but the extent to which the current findings are in agreement is unclear as survival estimates were not presented (13, 15) and associations with prognostic factors are not directly comparable (23). Finally, the current study differs from the aforementioned studies in that it focuses specifically on tumors > 1 mm in women; hence it is difficult to directly compare the findings.

A previous NOWAC study found that fair pigmentation was associated with thinner melanomas (11) and discussed whether this was due to increased melanoma awareness among those with high-risk phenotypes. Others have also suggested that lower melanoma-specific mortality among those with high-risk phenotypes may result from increased screening and overdiagnosis, resulting in thinner, less life-threatening tumors (17). As indications of higher risk of melanoma death among women with darker pigmentation and nevi were maintained among those with tumors > 1 mm, the current findings indicate that there may be biological mechanisms that might improve outcomes among those with high-risk phenotypes beyond awareness. Adjustment for education, as a proxy for socioeconomic status, did not modify the estimates, further discrediting the argument that differences in melanoma-specific mortality are due to differences in awareness by pigmentation.

Inverse associations were recently found between polygenic risk scores (PRSs) designed specifically for nevi and pigmentation, and melanoma-specific mortality (32). The melanocortin 1 receptor (MC1R) regulates skin and hair colour in humans by regulating eumelanin

Table II. Pigmentary characteristics and melanoma-specific death, stratified by number of large asymmetrical nevi, incident melanoma cases in the Norwegian Women and Cancer cohort (1991 to 2018) in women with tumors >1 mm

Variable	0 asymmetrical nevi >5 mm (>1 mm) HR (95% CI)[a]	≥1 asymmetrical nevi >5 mm (>1 mm) HR (95% CI)[a]	*p*-value for interaction
Hair colour			
Red/blonde/yellow	1	1	
Brown/dark brown/black	1.06 (0.70–1.61)	1.67 (0.72–3.91)	0.300
Eye colour			
Blue	1	1	
Grey/green/mixed/brown	1.24 (0.82–1.89)	1.56 (0.66–3.72)	0.382
Skin colour			
Light	1	1	
Medium/darker	1.02 (0.64–1.61)	1.91 (0.78–4.63)	0.076
Freckling when sunbathing			
Yes	1	1	
No	1.09 (0.69–1.74)	0.92 (0.39–2.13)	0.588
Pigmentary score			
Fair	1	1	
Medium/darker	0.97 (0.60–1.56)	1.96 (0.75–5.13)	0.056
Skin reaction to acute sun exposure[b]			
Red[c]	1	1	
Brown	1.30 (0.77–2.20)	2.86 (0.83–9.79)	0.184
Skin reaction to chronic sun exposure[b]			
Light brown/never brown	1	1	
Brown/deep brown	0.89 (0.55–1.44)	0.83 (0.33–2.13)	0.409

[a]Cox proportional hazards regression stratified by birth cohort, and with time since diagnosis as time scale adjusting for age at diagnosis, region of residence, and education. [b]Recorded for subsamples of the cohort. [c]Red with burning and blistering, and red. HR: hazard ratio; CI; confidence interval.

production (33), and is associated with both an elevated risk of melanoma development (1) and lower melanoma-specific mortality (4), particularly in women (34). MC1R modifies pigmentation through the microphthalmia-associated transcription factor (MITF), but the MITF also targets other genes, such as those which regulate DNA repair (4). It has been found that those with "R" variants are resistant to (α-MSH)-mediated DNA repair (35). As overexpression of DNA repair pathways in melanoma is reportedly associated with poor survival outcomes (4), the low expression of DNA repair genes among those with MC1R "R" variants may improve prognostic outcomes, which would be in line with the findings of the current study. In addition, the T allele of the interferon regulatory factor 4 (IRF4) gene is associated with high nevus counts in adolescents, but with low nevus counts in adults and with worse survival outcomes independent of associated phenotypic characteristics (5, 36). Thus, nevus count may serve as a proxy for IRF4, partially explaining the observed associations in the current study.

Strengths of the current study are the large, prospective population-based design, high response rate, and detailed melanoma information through CRN linkages. In the CRN, 99.8% of primary cutaneous melanomas are morphologically verified (25). Pigmentary factors were self-reported and some misclassification is likely; however, due to the prospective nature of this study, information was obtained before diagnosis. While socio-economic status (20) is associated with melanoma-specific mortality, it is unlikely that socio-economic divisions are along pigmentary lines in the current cohort. Finally, non-ethnic Norwegians have equal access to free healthcare and similar cancer survival outcomes in Norway (37), thus it is unlikely that the current findings were driven by non-ethnic Norwegians, who are more likely to be darker pigmented, having unequal access to care.

This study cannot exclude the possibility that the observed associations represent another unmeasured confounder. In addition, as this study conditioned on melanoma diagnosis, the current analysis may be affected by collider stratification bias (38). Those without traditional melanoma risk factors who develop thick melanomas may have some other, more potent, unobserved risk factor, which is both associated with developing melanoma and poor melanoma prognosis. While the current study did not have access to genetic data, a large twin study found an excess hereditary risk for melanoma (39). In addition, it has been suggested that a genetic predisposition to develop melanoma may be associated with lower melanoma-specific mortality irrespective of tumor thickness (32).

Despite the large dataset, there were few melanoma deaths, and some pigmentary factors were recorded in subsamples only, which may have affected some estimates. While the current study lacked information on treatments, treatment regimens did not change during this study period, except for the implementation of immune therapy for distant metastasis in 2014 (40), which is uncommon in our population. The results may have also been affected by terminal digit clustering in thickness data; however, terminal digit clustering increases proportions of tumors classified as T1 and T4 (41), so it is unlikely to affect the results of this study. In addition, while approximately 8% of participants had missing data regarding tumor thickness, this proportion was similar to that found in other studies (42, 43), and results were similar between the complete-case and multiple imputation analysis. Finally, the current study lacked data on ulceration status and sentinel node involvement, which limited its ability to classify participants using the tumor, node, metastasis staging system.

In conclusion, this study indicates that lighter pigmentation and having nevi may be associated with better melanoma-specific mortality in Norwegian women with melanomas > 1.0 mm thick. These results suggest that biological mechanisms related to pigmentation may also affect melanoma severity and prognosis beyond melanoma awareness. Given the few deaths, many of the individual estimates were not statistically significant. However, the results still trended towards those women with darker pigmentation having worse melanoma outcomes. More research is needed in larger studies to corroborate the current findings and to address knowledge gaps regarding biological mechanisms related to nevi, pigmentation, and melanoma-specific mortality, and how these patterns are modified by tumor thickness and histological subtype. However, the current findings could help to guide clinician awareness and follow-up among patients who do not display traditional melanoma risk factors.

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The authors have no conflicts of interest to declare.

REFERENCES

1. Berwick M, Buller DB, Cust A, Gallagher R, Lee TK, Meyskens F, et al. Melanoma epidemiology and prevention. Cancer Treat Res 2016; 167: 17–49.

2. Pho LN, Leachman SA. Genetics of pigmentation and melanoma predisposition. G Ital Dermatol Venereol 2010; 145: 37–45.
3. Whiteman DC, Brown RM, Purdie DM, Hughes M-C. Melanocytic nevi in very young children: The role of phenotype, sun exposure, and sun protection. J Am Acad Dermatol 2005; 52: 40–47.
4. Davies JR, Randerson-Moor J, Kukalizch K, Harland M, Kumar R, Madhusudan S, et al. Inherited variants in the MC1R gene and survival from cutaneous melanoma: a BioGenoMEL study. Pigment Cell Melanoma Res 2012; 25: 384–394.
5. Duffy DL, Iles MM, Glass D, Zhu G, Barrett JH, Höiom V, et al. IRF4 variants have age-specific effects on nevus count and predispose to melanoma. Am J Hum Genet 2010; 87: 6–16.
6. Ribero S, Davies JR, Requena C, Carrera C, Glass D, Rull R, et al. High nevus counts confer a favorable prognosis in melanoma patients. Int J Cancer 2015; 137: 1691–1698.
7. Rachakonda S, Srinivas N, Mahmoudpour SH, Garcia-Casado Z, Requena C, Traves V, et al. Telomere length and survival in primary cutaneous melanoma patients. Sci Rep 2018; 8: 10947.
8. Liu W, Dowling JP, Murray WK, McArthur GA, Thompson JF, Wolfe R, et al. Rate of growth in melanomas: characteristics and associations of rapidly growing melanomas. Arch Dermatol 2006; 142: 1551–1558.
9. Taylor NJ, Thomas NE, Anton-Culver H, Armstrong BK, Begg CB, Busam KJ, et al. Nevus count associations with pigmentary phenotype, histopathological melanoma characteristics and survival from melanoma. Int J Cancer 2016; 139: 1217–1222.
10. Li W-Q, Cho E, Weinstock MA, Li S, Stampfer MJ, Qureshi AA. Cutaneous nevi and risk of melanoma death in women and men: a prospective study. J Am Acad Dermatol 2019; 80: 1284–1291.
11. Ghiasvand R, Green AC, Sandanger TM, Weiderpass E, Robsahm TE, Veierød MB. Phenotypic characteristics and melanoma thickness in women. Acta Derm Venereol 2021; 101: adv00446.
12. Baumert J, Plewig G, Volkenandt M, Schmid-Wendtner MH. Factors associated with a high tumor thickness in patients with melanoma. Br J Dermatol 2007; 156: 938–944.
13. Mishra K, Barnhill RL, Paddock LE, Fine JA, Berwick M. Histopathologic variables differentially affect melanoma survival by age at diagnosis. Pigment Cell Melanoma Res 2019; 32: 593–600.
14. Rosso S, Sera F, Segnan N, Zanetti R. Sun exposure prior to diagnosis is associated with improved survival in melanoma patients: results from a long-term follow-up study of Italian patients. Eur J Cancer 2008; 44: 1275–1281.
15. Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricker A, Eberle C, et al. Sun exposure and mortality from melanoma. J Natl Cancer Inst 2005; 97: 195–199.
16. Paddock LE, Lu SE, Bandera EV, Rhoads GG, Fine J, Paine S, et al. Skin self-examination and long-term melanoma survival. Melanoma Res 2016; 26: 401–408.
17. Autier P, Funck-Brentano E, Aegerter P, Boniol M, Saiag P. Re: High nevus counts confer a favorable prognosis in melanoma patients by S ribero and co-workers, published in the International Journal of Cancer, 2015 (online 21 march 2015). Int J Cancer 2015; 137: 3006–3007.
18. Oliveria SA, Christos PJ, Halpern AC, Fine JA, Barnhill RL, Berwick M. Evaluation of factors associated with skin self-examination. Cancer Epidemiol Biomarkers Prev 1999; 8: 971–978.
19. Olsen CM, Thompson BS, Green AC, Neale RE, Whiteman DC, Sun ftQ, et al. Sun protection and skin examination practices in a setting of high ambient solar radiation: a population-based cohort study. JAMA Dermatol 2015; 151: 982–990.
20. Eriksson H, Lyth J, Månsson-Brahme E, Frohm-Nilsson M, Ingvar C, Lindholm C, et al. Low level of education is associated with later stage at diagnosis and reduced survival in cutaneous malignant melanoma: a nationwide population-based study in Sweden. Eur J Cancer 2013; 49: 2705–2716.
21. Watts CG, McLoughlin K, Goumas C, van Kemenade CH, Aitken JF, Soyer HP, et al. Association between melanoma detected during routine skin checks and mortality. JAMA Dermatol 2021; 157: 1425–1436.
22. De Giorgi V, Scarfi F, Gori A, Maida P, Trane L, Silvestri F, et al. Nevi and Breslow thickness in melanoma: sex differences? Melanoma Res 2020; 30: 179–184.
23. Li WQ, Cho E, Wu S, Li S, Matthews NH, Qureshi AA. Host Characteristics and risk of incident melanoma by breslow thickness. Cancer Epidemiol Biomarkers Prev 2019; 28: 217–224.
24. Lund E, Dumeaux V, Braaten T, Hjartåker A, Engeset D, Skeie G, et al. Cohort profile: The Norwegian Women and Cancer Study – NOWAC – Kvinner og kreft. Int J Epidemiol 2008; 37: 36–41.
25. Cancer Registry of Norway. Cancer in Norway 2020 – Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway, 2021.
26. 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: 1–9.
27. World Health Organization. (1957). Manual of the international statistical classification of diseases, injuries, and causes of death : based on the recommendations of the seventh revision Conference, 1955, and adopted by the ninth World Health Assembly under the WHO Nomenclature Regulations. World Health Organization. https://apps.who.int/iris/handle/10665/42900.
28. World Health Organization. (2013). International classification of diseases for oncology (ICD-O), 3rd ed., 1st revision. World Health Organization. https://apps.who.int/iris/handle/10665/96612.
29. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017; 67: 93-99.
30. Veierød MB, Weiderpass E, Thörn M, Hansson J, Lund E, Armstrong B, et al. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst 2003; 95: 1530–1538.
31. Damsky WE, Theodosakis N, Bosenberg M. Melanoma metastasis: new concepts and evolving paradigms. Oncogene 2014; 33: 2413–2422.
32. Seviiri M, Scolyer RA, Bishop DT, Newton-Bishop JA, Iles MM, Lo SN, et al. Higher polygenic risk for melanoma is associated with improved survival in a high ultraviolet radiation setting. J Transl Med 2022; 20: 403.
33. Ainger SA, Jagirdar K, Lee KJ, Soyer HP, Sturm RA. Skin pigmentation genetics for the clinic. Dermatology 2017; 233: 1–15.
34. Lira FE, Podlipnik S, Potrony M, Tell-Martí G, Calbet-Llopart N, Barreiro A, et al. Inherited MC1R variants in patients with melanoma are associated with better survival in women. Br J Dermatol 2020; 182: 138–146.
35. Kadekaro AL, Leachman S, Kavanagh RJ, Swope V, Cassidy P, Supp D, et al. Melanocortin 1 receptor genotype: an important determinant of the damage response of melanocytes to ultraviolet radiation. FASEB J 2010; 24: 3850–3860.
36. Rayner JE, McMeniman EK, Duffy DL, De'Ambrosis B, Smithers BM, Jagirdar K, et al. IRF4 rs12203592*T/T genotype is associated with nodular melanoma. Melanoma Res 2019; 29: 445–446.
37. Thøgersen H, Møller B, Robsahm TE, Babigumira R, Aaserud S, Larsen IK. Differences in cancer survival between immigrants in Norway and the host population. Int J Cancer 2018; 143: 3097–3105.
38. Stensrud MJ, Valberg M, Røysland K, Aalen OO. Exploring selection bias by causal frailty models: the magnitude matters. Epidemiol 2017; 28: 379–386.
39. Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, et al. Familial risk and heritability of cancer among twins in Nordic countries. JAMA 2016; 315: 68–76.
40. Jacobsen KD, Akslen LA, Busch C, Bachmann IM, Fjøsne HE, Helsing P, et al. National action program with guidelines for diagnostics, treatment and follow-up of malignant melanomas. Oslo, Norway: Norwegian Directorate of Health, 2019.
41. Veierød MB, Page CM, Aaserud S, Bassarova A, Jacobsen KD, Helsing P, et al. Melanoma staging: varying precision and terminal digit clustering in Breslow thickness data is evident in a population-based study. J Am Acad Dermatol 2018; 79: 118–125.e1.
42. Lindholm C, Andersson R, Dufmats M, Hansson J, Ingvar C, Möller T, et al. Invasive cutaneous malignant melanoma in Sweden, 1990–1999. A prospective, population-based study of survival and prognostic factors. Cancer 2004; 101: 2067–2078.
43. Chen ML, de Vere Hunt IJ, John EM, Weinstock MA, Swetter SM, Linos E. Differences in thickness-specific incidence and factors associated with cutaneous melanoma in the US from 2010 to 2018. JAMA Oncol 2022; 8: 755–759.