Human Reproduction, Vol.37, No.5, pp. 1059–1068, 2022
Advance Access Publication on February 17, 2022 https://doi.org/10.1093/humrep/deac029

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Reproductive factors, hormone use, and incidence of melanoma in a cohort of US Radiologic Technologists

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Submitted on June 30, 2021; resubmitted on January 5, 2022; editorial decision on January 27, 2022

STUDY QUESTION: Are reproductive factors and exogenous hormone use associated with incidence of cutaneous melanoma while accounting for ultraviolet radiation (UVR) exposure across different life periods and sun sensitivity factors?

SUMMARY ANSWER: Earlier age at menarche and late age at first birth, but not other estrogen-related factors were associated with an increased incidence rate of melanoma, with higher risks observed for earlier age at menarche and light hair color at age 15 years.

WHAT IS KNOWN ALREADY: Although estrogens have been recognized as photosensitizing, previous studies have reported inconsistent findings for the association of melanoma with estrogen-related factors. Most have not collected detailed skin cancer risk factors and have not thoroughly investigated effect modification by ambient UVR and sun sensitivity.

STUDY DESIGN, SIZE, DURATION: Participants in the US Radiologic Technologists study, an occupational cohort of 146 022 radiologic technologists (73% women), were included and followed during the four time periods (1983–1989, 1994–1998, 2003–2005 and 2012–2014).

PARTICIPANTS/MATERIALS, SETTING, METHODS: Non-Hispanic white female participants who completed both the second (baseline) and third questionnaires, and did not report having cancer (except keratinocyte carcinoma) at baseline, were included and followed from their age at completion of the second (baseline) questionnaire until the earlier of first primary cancer diagnosis, including invasive melanoma of the skin, or completion of either the third or fourth questionnaire. Reproductive and exogenous hormonal factors were ascertained from the second (baseline) questionnaire, which also collected information on demographic, lifestyle factors and sun sensitivity factors. Ambient UVR was assigned by linking geocoded residential locations, based on self-reported residential history information collected from the third questionnaire to satellite-based ambient UVR data from the National Aeronautics and Space Administration's Total Ozone Mapping Spectrometer database. To examine the association of reproductive factors, exogenous hormone use, and first primary invasive melanoma of the skin, we used Poisson regression to calculate rate ratios (RRs) and 95% likelihood-based CIs, adjusting for attained age, birth cohort, lifetime average annual ambient UVR, contraceptives and menopausal hormone therapy use. To address the effect modification of ambient UVR exposure and sun sensitivities on melanoma risk, we conducted likelihood-ratio tests for multiplicative interaction.

MAIN RESULTS AND THE ROLE OF CHANCE: Over a median follow-up time of 17.1 years, 0.95% of eligible participants had an incident first primary melanoma (n = 444). Higher melanoma incidence rates were observed in participants with older attained age, blue/green/gray eye color, blonde/red/auburn natural hair color at age 15, fair skin complexion, and higher UVR. We found an increased incidence rate of melanoma in women who experienced menarche at an earlier age (13, 12 and <12 years vs ≥14 years: RR = 1.48, 95% CI = 1.11–1.98; 1.19, 0.89–1.61; 1.26, 0.93–1.73), and in women with older age at first birth (25–29 and ≥30 years vs <25 years; 1.09, 0.86–1.39; 1.48, 1.12–1.95; *P*-value for trend = 0.006). However, no significant association was observed for other reproductive factors, and for all exogenous hormone use. The associations of melanoma incidence for most reproductive factors and exogenous hormone use were not modified by ambient UVR, eye color, natural hair color at age 15 and skin complexion. The exception was that natural hair color

at age 15 modified the associations of melanoma for age at menarche (*P*-value for interaction = 0.004) and age at first birth among parous women (0.005). In participants with blonde/red/auburn natural hair color at age 15, we found increased risk of melanoma among women who experienced menarche at age 13, 12 and <12 years (vs ≥14 years: RR = 3.54, 95% CI = 1.98–6.90; 2.51, 1.37–4.98; 2.66, 1.41–5.36, respectively; *P*-value for trend = 0.10). However, the association between age at menarche and melanoma was null in participants with brown/black natural hair color at age 15.

LIMITATIONS, REASONS FOR CAUTION: Information on reproductive history and exogenous hormone use was self-reported. We did not have information on specific doses or formulations of exogenous hormone medications or breastfeeding.

WIDER IMPLICATIONS OF THE FINDINGS: Women residing in areas of high ambient UVR and those with blonde/red/auburn natural hair color may constitute an additional high-risk group in need of more frequent skin cancer screening. Identifying susceptible periods of exposure or factors that modify UVR susceptibility may aid in guiding more targeted guidelines for melanoma prevention.

STUDY FUNDING/COMPETING INTEREST(S): This research was supported by the Intramural Research Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Authors declare no conflict of interest.

TRIAL REGISTRATION NUMBER: N/A.

Key words: reproductive factors / exogenous hormone use / ultraviolet radiation / cutaneous melanoma / epidemiology / estrogen

Introduction

Cutaneous melanoma is the fifth most common cancer in the USA with an estimated 106 110 new cases annually in 2021 (Siegel *et al.*, 2021). Melanoma also has one of the fastest growing incidence rates (Henley *et al.*, 2020), having increased by at least 1.68% annually between 2005 and 2015 in the USA (Thrift and Gudenkauf, 2020) with analogous increases in Australia and northern Europe (Bray *et al.*, 2018). Established risk factors for melanoma include increased number of nevi, light pigmentary traits, family history of melanoma, history of previous skin cancer (Armstrong *et al.*, 2017). While exposure to ultraviolet radiation (UVR) is considered as the main preventable cause of melanoma, the nature of the relationship is complex (Armstrong and Cust, 2017). The relative importance of dose and timing of exposure have been investigated (Gandini *et al.*, 2005), with strong positive associations found for intermittent sun exposure, weaker or inconsistent associations for increasing cumulative lifetime UVR exposure, and both increased and reduced risks for occupational sun exposure, and evidence of increased susceptibility for childhood sun exposure. Melanoma is characterized by a distinct sex- and age-distribution (Olsen *et al.*, 2020), with an age-specific incidence rate generally greater in women than men until the age of 45–49 years after which it is higher for men (Liu *et al.*, 2013). Possibly due to the photosensitizing properties of estrogen (Richarz *et al.*, 2017), female reproductive factors and exogenous hormone use have also been suggested to play a role in melanoma etiology (Donley *et al.*, 2019).

A number of epidemiologic studies have investigated the role of estrogen-related factors and risk of melanoma (Gandini *et al.*, 2011; Sun *et al.*, 2020; Tang *et al.*, 2020). However, they were all set in locations with relatively little variation in UVR, and few have focused on the photosensitizing properties of estrogen-related factors by examining interactions between UVR, estrogen-related factors and risk of melanoma. A number of case–control studies reported positive associations of reproductive factors and exogenous hormone use with risk of melanoma, but case–control studies might be subject to recall bias with respect to well-known skin cancer risk factors (Gandini *et al.*, 2011; Sun *et al.*, 2020; Tang *et al.*, 2020). Several prospective cohort studies have investigated estrogen-related factors in association with melanoma, but few have reported whether the associations between estrogen-related factors and melanoma vary by UVR exposure and personal sun sensitivity. Exceptions included studies in France (Kvaskoff *et al.*, 2011; Cervenka *et al.*, 2018, 2019), Norway (Botteri *et al.*, 2017) and 10 European countries (Cervenka *et al.*, 2020) which reported no evidence of effect modification between UVR and estrogen-related factors for melanoma. A recent study in US women exposed to substantial variation in ambient UVR, was the first to show effect modification by age at menarche for the relationship between ambient UVR and melanoma risk (Donley *et al.*, 2019), suggesting a photocarcinogenic role of estrogen exposure in early life. However, this study lacked information on ambient UVR exposure in childhood and personal sun sensitivity factors.

The objective of this study is to examine the association between reproductive factors, exogenous hormone use, and first primary invasive melanoma of the skin. We use data from the US Radiologic Technologists (USRT) study, which includes a geographically dispersed set of women exposed to a wide range of ambient UV radiation. The USRT includes comprehensive information on UVR exposure across different life periods, personal sun sensitivity and lifestyle factors.

Materials and methods

Overview

The USRT is an occupational cohort of 146 022 radiologic technologist (73% women) who were certified by the American Registry of Radiological Technologists for at least 2 years between 1926 and 1982 (https://radtechstudy.nci.nih.gov). Previous analyses in the USRT found no association between risks of melanoma number of years worked (Freedman *et al.*, 2003; Liu *et al.*, 2014). Methods used in assembling and following up the cohort have been detailed previously (Kitahara *et al.*, 2018). Briefly, self-administered questionnaires were mailed to cohort members during the following four time periods: 1983–1989, 1994–1998, 2003–2005 and 2012–2014. A second questionnaire (which inquired about most estrogen-related factors) was mailed between 1994 and 1998 to all living and located technologists

(N = 126 628) and completed by 90 972 technologists (72%). A third questionnaire, administered by mail or phone between 2003 and 2005, only to those all living and located technologists who answered either the first or second questionnaires (N = 101 694), was completed by 73 838 technologists (73%) and, collected information on residential location over the lifetime (for ages <13, 13–19, 20–39, 40–64 and 65+ years) and medical history, including any diagnoses of melanoma. A fourth questionnaire was administered between 2012 and 2013 to all living and located technologists who responded to either the first or second questionnaires (N = 93 787) and was completed by 58 587 technologists (62%).

Informed consent was obtained to collect medical records. The USRT study has been annually approved by human subjects' review boards at the University of Minnesota (Minneapolis, MN) and the National Cancer Institute (Bethesda, MD).

Study population

The study population included white female participants who completed both the second (baseline) and third questionnaires and did not report having cancer (except keratinocyte carcinoma, KC) at baseline. Due to insufficient statistical power in races other than non-Hispanic whites (1 melanoma case among 2505 non-white participants), we only included non-Hispanic whites. We further excluded participants without ambient UVR information. Participants (N = 46 544) were followed from their age at completion of the second questionnaire until the earlier of first primary cancer diagnosis, including invasive melanoma of the skin, or completion of (either the third or fourth) questionnaire. Questionnaire response pattern (whether participant completed the fourth questionnaire) is considered in analyses.

Case ascertainment

Incident melanoma, defined as diagnosis of a first primary invasive melanoma of the skin after the second questionnaire, was ascertained from either the third or fourth questionnaire through self-report. Pathology reports and other confirmatory medical records were requested to validate the self-reported melanomas. Medical records to confirm invasive melanoma diagnosis were successfully obtained for 219 women (49.3%). Our primary analyses included the remaining 225 for whom medical record confirmation could not be obtained because our results did not substantially differ after restricting to medically confirmed cases.

Exposure assessment

Reproductive and exogenous hormonal factors (age at menarche and at first birth, parity, infertility, menopausal status, reason for menopause, age at menopause, mother's use of diethylstilbestrol and estrogen-related medication use) were ascertained from the second (baseline) questionnaire, which also collected information on skin complexion, eye color, hair color at age 15, Gaelic/Celtic ancestry, previous KC diagnosis, family history of melanoma (first degree relative), smoking history, alcohol use, BMI, education, marital status, coffee consumption, and cumulative absorbed occupational radiation dose to the skin of the head and neck (mGy). The lifetime cumulative number of menstrual cycles was calculated from age at menarche to either age at menopause or age at completion of the second questionnaire (years). We computed menstrual cycles due to oral contraceptives (OC) use as 1-year duration (0, 1, 3, 5 or 10 years), and took all available variables into account, considering that each pregnancy, stillbirth, miscarriage, or abortion, resulted in an absence of cycles for a period of 36, 28 and both 12 weeks, respectively (Chavez-MacGregor *et al.*, 2005).

Ambient UVR was assigned by linking geocoded residential locations, based on self-reported residential history information collected from the third questionnaire to satellite-based ambient UVR data from the National Aeronautics and Space Administration's Total Ozone Mapping Spectrometer database. This database provides estimates of cloud-adjusted daily noontime ambient UVR of 305 nm on a 1^0 latitude × 1^0 longitude resolution, about 110 × 85 km in the central USA. Satellite-based annual estimates of UVR over the USA have varied little since the start of measurements in the late 1970s (except for small fluctuations during 11-year solar cycles), thus daily noontime estimates were averaged over years 1978–1993 for each location to construct stable estimates. As surface UVR is strongest during the summer, we also calculated ambient UVR of 305 nm for the month of July. We then generated a weighted average lifetime ambient UVR exposure (annual and July, separately) accounting for a subject's number of years in each age period, and hereafter refer to this measure as ambient UVR.

Statistical analysis

To examine the association of reproductive factors, exogenous hormone use, and first primary invasive melanoma of the skin, we used Poisson regression to calculate rate ratios (RRs) and 95% likelihood-based CIs. To perform these analyses, we generated a table of person–years and melanoma cases based on the following stratification factors: age at menarche, number of live births, age at first birth among parous women, menopausal status at baseline, number of menstrual cycles, age at natural menopause, age at surgical menopause, maternal use of diethylstilbestrol, OC use, duration of OC use, menopausal hormone therapy (MHT) use, duration of MHT use, MHT type (never, unopposed estrogen or estrogen/progestin), number of removed ovaries, attained age, birth cohort, education, marital status, BMI, physical activity, smoking history, drinking status, coffee consumption, skin complexion, eye color, hair color at age 15, Gaelic/Celtic ancestry, previous diagnosis of KC, family history of melanoma (1st degree relative), questionnaire response pattern (whether participants completed the fourth questionnaire in 2012–2014), cumulative absorbed occupational radiation dose to the skin of the head and neck, average annual lifetime ambient UVR exposure, other reproductive factors and exogenous hormone use. We included a priori, attained age, birth cohort (1905–1940, 1941–1945, 1946–1950, 1951–1955, 1956–1966), lifetime average annual ambient UVR (Quartile 1–4), ever use of OC for reproductive factors, and ever use of MHT (for OC use models) for exogenous hormones because these are established risk factors for melanoma or have been used in previous studies (Armstrong *et al.*, 2017). We additionally considered the remaining factors as potential confounders because they may be associated with the exposure of interest and melanoma risk but are not thought to be on the causal pathway. However, their inclusion in the model did not meaningfully change the results. To investigate whether the associations between estrogen-related factors and melanoma vary by UVR exposure and

personal sun sensitivity factors, we conducted likelihood-ratio tests for multiplicative interaction between estrogen-related factors and melanoma risk by ambient UVR (low: <28.2 J/m^2 vs high: ≥28.2 J/m^2), eye color (blue/green/gray vs hazel/brown/black), natural hair color at age 15 (blonde/red/auburn vs brown/black), and skin complexion (fair vs medium/dark).

We conducted several sensitivity analyses. We stratified by early-onset (age at diagnosis <55 years) vs late-onset (≥55) melanoma, which did not reveal any significant differences in their relationships with reproductive factors or exogenous hormone use. We also conducted sensitivity analyses using erythemal UVR exposure in July and including participants with missing data on ambient UVR (data not shown because they did not substantially affect our results). We evaluated different exposure periods (for ages <13, 13–19, 20–39, 40–64 or 65+ years old) of UVR for testing interaction with reproductive factors and hormone use, which did not alter our results meaningfully (data not shown). Missing values were classified as separate categories and included as indicator variables in the models. We also conducted complete case analysis. Adjustment for multiple comparisons may not be necessary in the present analysis with defined hypotheses (Rothman, 1990). All statistical tests were two-sided with a specific Type-I error of 0.05, and analyses were performed in Epicure (Risk Sciences International Inc., Ottawa, Canada).

Results

The study population included 46 544 non-Hispanic white women who did not report having cancer (except for KC) at baseline. Over a median follow-up time of 17.1 years, 0.95% of eligible participants had an incident primary melanoma (n = 444). Higher melanoma incidence rates were observed in participants with older attained age, blue/green/gray eye color, blonde/red/auburn natural hair color at age 15, fair skin complexion and higher UVR (Table I).

We found an increased incidence rates of melanoma in women who experienced menarche at age 13, 12 and <12 years (vs ≥14 years: RR = 1.48, 95% CI = 1.11–1.98; 1.19, 0.89–1.61; 1.26, 0.93–1.73), and in women with older age at first birth (25–29 and ≥30 years vs <25 years; 1.09, 0.86–1.39; 1.48, 1.12–1.95; *P*-value for trend <0.001) (Table II). However, no significant association was observed for other reproductive factors, and for all exogenous hormone use (Table III). Similar results were observed using complete case analysis (Supplementary Tables SI and SII).

The associations of melanoma incidence for most reproductive factors and exogenous hormone use were not modified by ambient UVR, eye color, natural hair color at age 15 and skin complexion (Supplementary Tables SIII, SIV, SV and SVI). The exception was that natural hair color at age 15 modified the associations of melanoma for age at menarche (*P*-value for interaction = 0.004) and age at first birth among parous women (0.005).

We investigated whether the associations between estrogen-related factors and melanoma vary by UVR exposure and personal sun sensitivity factors. In participants with blonde/red/auburn natural hair color at age 15, we found increased incidence rates of melanoma among women who experienced menarche at age 13, 12 and <12 years (vs ≥14 years: RR = 3.54, 95% CI = 1.98–6.90; 2.51, 1.37–4.98; 2.66, 1.41–5.36, respectively; *P*-value for trend = 0.10). The association between age at menarche and melanoma was null in participants with brown/black natural hair color at age 15 (Fig. 1). Incidence rates of melanoma for earlier age at menarche were also higher in participants exposed to high UVR exposure (≥28.2 J/m^2; 13, 12 and <12 years vs ≥14 years: RR = 1.77, 95% CI = 1.16–2.79; 1.62, 1.06–2.55; 1.60, 1.01–2.58, respectively), and in women with high sun sensitivities, including blue/green/gray eye color (13, 12 and <12 years vs ≥14 years: 1.65, 1.11–2.53; 1.42, 0.95–2.20; 1.25, 0.79–2.00, respectively), and fair skin complexion (1.55, 1.09–2.24; 1.38, 0.96–2.01; 1.17, 0.79–1.75).

Discussion

Our study prospectively evaluated the association between reproductive factors, exogenous hormone uses and melanoma incidence in a large nationwide US population with detailed information on a comprehensive list of melanoma risk factors including lifetime ambient UVR exposure based on location of residence, and personal sun sensitivity. Women who experienced menarche at earlier age and late age at first birth were associated with increased incidence rates of melanoma. However, no association was found for other reproductive factors and all exogenous hormone use. The positive association between earlier age at menarche and melanoma was modified by natural hair color at age 15, with a stronger relationship among women with blonde/red/auburn natural hair color. This is the first study to show effect modification by UVR exposure and personal sun sensitivities for the association between age at menarche and melanoma incidence.

Age at menarche

Incidence rate of melanoma was higher for earlier age at menarche, and appeared to be stronger in women who exposed to high ambient UVR and in women with high sun sensitivities, supporting the hypothesis that estrogen exposure is photocarcinogenic (Stern, 1998). This finding of the association between earlier age at menarche and high melanoma risk agrees with several cohort studies in the USA (Donley *et al.*, 2019; Fuhrman *et al.*, 2021), Denmark (Kaae *et al.*, 2007), France (Kvaskoff *et al.*, 2011), and Australia (Olsen *et al.*, 2021).

Early-life UVR exposure has been found to be strongly associated with an increased risk of melanoma (Whiteman *et al.*, 2001; Wu *et al.*, 2014). Our findings of effect modification for age at menarche, but not age at menopause or MHT use, highlighted the importance of early-life estrogen exposure for melanoma risk, especially in women living in locations with high levels of ambient UVR, and those with high sun sensitivities. Associations between age at menarche and melanoma risk appeared to be stronger in sun sensitive women categorized by light hair color compared to those with fair skin complexion. Misclassification in self-reported skin complexion may contribute, in part, to weaker associations for reproductive factors in fair skin (Reeder *et al.*, 2010; Eilers *et al.*, 2013). Behavioral factors such as tanning, related to UVR exposure may result in biased estimates if they are also associated with ambient UVR in this study. However, in a population-based study of US women, indoor tanning was slightly higher in locations with both high and low

Table I Distribution of baseline characteristics of 46 544 non-Hispanic white women in the US Radiologic Technologists study.

Characteristic	Person–years[a]	No. with melanoma	Crude rate (per 10^5 person–years)	95% CI
All	698 456	444	63.6	(57.9, 69.7)
Attained age, years				
35 to <50	230 007	131	57.0	(47.8, 67.3)
50 to <55	152 270	96	63.1	(51.3, 76.5)
55 to <60	129 036	86	66.7	(53.5, 81.8)
60 to <65	86 665	58	66.9	(51.2, 85.6)
65 to <70	52 088	39	74.9	(53.8, 101)
70–102	48 391	34	70.3	(49.2, 96.6)
Year of birth				
1905–1940	115 501	76	65.8	(52.1, 81.7)
1941–1945	97 323	60	61.7	(47.3, 78.6)
1946–1950	154 484	110	71.2	(58.7, 85.4)
1951–1955	201 466	123	61.1	(50.9, 72.5)
1956–1966	129 682	75	57.8	(45.7, 72.0)
Eye color				
Blue/green/gray	317 114	221	69.7	(60.9, 79.3)
Hazel/brown/black	368 965	210	56.9	(49.6, 65.0)
Unknown/missing	12 377	13	105	(57.8, 173)
Natural hair color at age 15[b]				
Blonde/red/auburn	155 266	149	96.0	(81.4, 112)
Brown/black	531 488	285	53.6	(47.6, 60.1)
Unknown/missing	11 702	10	85.5	(42.8, 150)
Skin color				
Fair	360 336	286	79.4	(70.5, 88.9)
Medium/dark	329 942	150	45.5	(38.6, 53.1)
Unknown/missing	8179	8	97.8	(44.7, 182)
Average lifetime annual erythemal UVR,[c] J/m^2				
Quartile 1 (lowest)	175 327	101	57.6	(47.1, 69.5)
Quartile 2	179 491	118	65.7	(54.6, 78.3)
Quartile 3	170 910	100	58.5	(47.8, 70.7)
Quartile 4 (highest)	172 728	125	72.4	(60.4, 85.8)

UVR, ultraviolet radiation.
[a]Median follow-up time = 17.1 years in all women, and 8.0 years in 444 melanoma cases.
[b]Blonde/red/auburn included blonde and red or auburn; brown/black included light brown, dark brown/brunette and black.
[c]Quartile 1 < 24.8 J/m^2; Quartile 2 = 24.8–28.2 J/m^2; Quartile 3 = 28.2–36.8 J/m^2 and Quartile 4 > 36.83 J/m^2.

ambient UVR (Choi *et al.*, 2010), which would be expected to have little impact on the overall estimated association between ambient UVR and melanoma risk.

Age at first birth and other reproductive factors and exogenous hormone use

The hormonal mechanism is controversial, though there seems to be a relationship between older age at first birth and melanoma incidence. Støer *et al*. and Kaae *et al*. both suggested lifestyle factors, as proxies for UVR exposure, were a more likely explanation. For instance, having one's first child at an older age may be associated with greater frequency of sun exposure, intensity of sun exposure and number of sunburns incurred during a critical risk period.

The null associations of melanoma incidence with most reproductive factors and exogenous hormone use from this study are consistent with the US Women's Health Initiative randomized controlled trials (RCTs) lack of association with MHT use (Tang *et al.*, 2011). However, in contrast to the current study, two recent meta-analyses showed MHT was associated with higher risks of melanoma (Sun *et al.*, 2020; Tang *et al.*, 2020). Also in contrast to the current study, number of live births was associated with lower risks of melanoma in a Danish cohort (Kaae *et al.*, 2007). These differences may be due to

Table II Reproductive factors and risk of malignant melanoma among 46 544 non-Hispanic white women in the US Radiologic Technologists study.

	Person–years	No. with melanoma[a]	RR[b,c]	95% CI
Age at menarche, years				
≥14	132 385	68	1	
13	200 240	151	1.48	(1.11, 1.98)
12	206 811	126	1.19	(0.89, 1.61)
<12	150 294	97	1.26	(0.93, 1.73)
Number of live births				
<2	229 194	138	1	
2	266 160	190	1.20	(0.96, 1.50)
≥3	192 747	113	0.97	(0.76, 1.25)
Age at first birth among parous women,[d] years				
<25	230 884	134	1	
25–29	219 915	135	1.09	(0.86, 1.39)
≥30	103 825	86	1.48	(1.12, 1.95)
Menopausal status at baseline				
Premenopausal	408 516	264	1	
Postmenopausal, natural	119 458	67	0.72	(0.51, 1.01)
Postmenopausal, surgical	148 015	103	0.94	(0.71, 1.22)
Cumulative number of menstrual cycles				
Quartile 1 (lowest)	105 814	70	1	
Quartile 2	103 718	71	1.04	(0.75, 1.45)
Quartile 3	105 430	77	1.08	(0.78, 1.51)
Quartile 4 (highest)	104 507	68	0.93	(0.65, 1.33)
Age at natural menopause,[e] years				
<50	57 345	32	1	
≥50	58 001	34	0.96	(0.57, 1.63)
Age at surgical menopause[f]				
<40 years	68 650	40	1	
40–44 years	31 880	28	1.42	(0.86, 2.31)
≥45	31 189	20	1.04	(0.57, 1.84)

RR, rate ratio.
[a]Numbers may be inconsistent because of missing values.
[b]Adjusted for age, birth cohort (1905–1940, 1941–1945, 1946–1950, 1951–1955, 1956–1966), lifetime average annual ambient ultraviolet radiation (Quartile 1–4), and contraceptives use (never, ever).
[c]All *P*-values for trend were >0.05, except age at first birth among parous women (0.006).
[d]Restricted to 37 932 parous women.
[e]Restricted to 8259 postmenopausal women reporting natural menopause.
[f]Restricted to 10 463 postmenopausal women reporting surgical menopause.

different sun-sensitivities in the populations or lifestyle/occupational factors that relate to sun exposure (e.g. indoor vs outdoor occupation). The null associations in the current study between age at menopause and melanoma were not consistent with the study of Donley *et al.* (2019) which found a significantly increased risk. This may be due to difference in study populations (radiological technologists in the whole USA vs older individuals in six states (California, Florida, Pennsylvania, New Jersey, North Carolina and Louisiana) or in two metropolitan areas (Atlanta, Georgia and Detroit, Michigan)), or possibly by chance since the current study has fewer melanoma cases.

Our study has several limitations beyond those previously discussed. Information on reproductive history and exogenous hormone use was self-reported, as were cases of melanoma, though this cohort of medical workers may have reported their medical history more accurately than women in the general US population. USRT studies have shown a high positive predictive value for melanoma (86.0%) (Sigurdson *et al.*, 2003), and a relatively low rate of under-reporting of melanoma (22.2%) (Freedman *et al.*, 2006). In addition, our results did not substantially differ between medically confirmed cases and self-reported cases. Our results should be interpreted with caution because they relied on recall of reproductive factors from adolescence. However, previous population-based studies have found moderate-to-strong agreement in recall of age at menarche (Cooper *et al.*, 2006; Lundblad and Jacobsen, 2017), and strong agreement for reproductive factors

Table III Exogenous hormone uses and risk of malignant melanoma among 46 544 non-Hispanic white women in the US Radiologic Technologists study.

	Person–years	No. with melanoma[a]	RR[c]	95% CI
OC use[b1]				
Never users	164 110	103	1	
Ever users	531 337	339	1.03	(0.82, 1.30)
Duration of OC use in ever users[b1]				
Never	164 110	103	1	
<1 year	54 073	29	0.86	(0.56, 1.29)
1–2 years	97 523	54	0.90	(0.64, 1.25)
3–4 years	114 459	76	1.08	(0.79, 1.46)
5–9 years	154 966	106	1.11	(0.84, 1.47)
≥10 years	103 996	71	1.10	(0.80, 1.50)
MHT[b2]				
Never users	486 821	306	1	
Ever users	207 270	136	0.98	(0.78, 1.24)
Past users	38 002	26	1.03	(0.66, 1.54)
Current users	164 186	104	0.94	(0.73, 1.21)
Duration of MHT use in ever users[b2]				
Never	486 821	306	1	
<5 year	108 894	73	1.01	(0.76, 1.32)
5–9 years	46 369	27	0.86	(0.56, 1.28)
≥10 years	45 051	29	0.94	(0.61, 1.40)
MHT type[b2]				
Never	486 821	306	1	
Unopposed estrogen	84 754	64	1.13	(0.84, 1.50)
Estrogen/progestin	118 517	66	0.83	(0.61, 1.10)
MHT use in women with natural menopause[b2,d]				
MHT use				
Never users	48 622	24	1	
Ever users	70 425	43	1.30	(0.78, 2.19)
Past users	15 447	6	0.79	(0.29, 1.81)
Current users	53 491	36	1.47	(0.86, 2.54)
Duration of MHT use in ever users				
Never	48 622	24	1	
<5 year	43 578	29	1.49	(0.85, 2.63)
≥5 years	24 907	13	1.04	(0.51, 2.03)
MHT use in women with hysterectomy[b2,e]				
MHT use				
Never users	44 143	30	1	
Ever users	103 316	73	0.90	(0.58, 1.43)
Past users	13 341	10	0.95	(0.43, 1.92)
Current users	88 001	61	0.89	(0.57, 1.42)
Duration of MHT use in ever users				
Never	44 143	30	1	
<5 year	40 662	30	0.99	(0.59, 1.66)
≥5 years	60 338	41	0.82	(0.50, 1.37)
MHT ever used by number of ovaries removed[b2]				
No ovary removed				
Never MHT users	31 033	16	1	
Ever MHT users	29 820	23	1.02	(0.50, 2.12)
1 ovary removed				
Never MHT users	8652	11	1	

(continued)

Table III Continued

	Person–years	No. with melanoma[a]	RR[c]	95% CI
Ever MHT users	11 120	7	0.49	(0.18, 1.31)
2 ovaries removed				
Never MHT users	5972	4	1	
Ever MHT users	63 796	44	0.98	(0.39, 3.27)
Mother took diethylstilbestrol				
No	560 070	352	1	
Yes	12 199	10	1.32	(0.66, 2.36)

RR, rate ratio; OC, oral contraceptives; MHT, menopausal hormone therapy.
[a]Numbers may be inconsistent because of missing values.
[b1]Adjusted for age, birth cohort (1905–1940, 1941–1945, 1946–1950, 1951–1955, 1956–1966), lifetime average annual ambient UVR (Quartile 1–4), and MHT use (never, ever).
[b2]Adjusted for age, birth cohort (1905–1940, 1941–1945, 1946–1950, 1951–1955, 1956–1966), lifetime average annual ambient UVR (Quartile 1–4), and OC use (never, ever).
[c]All *P*-values for trend were >0.05.
[d]Restricted to 8259 postmenopausal women reporting natural menopause.
[e]Restricted to 10 463 postmenopausal women reporting surgical menopause.

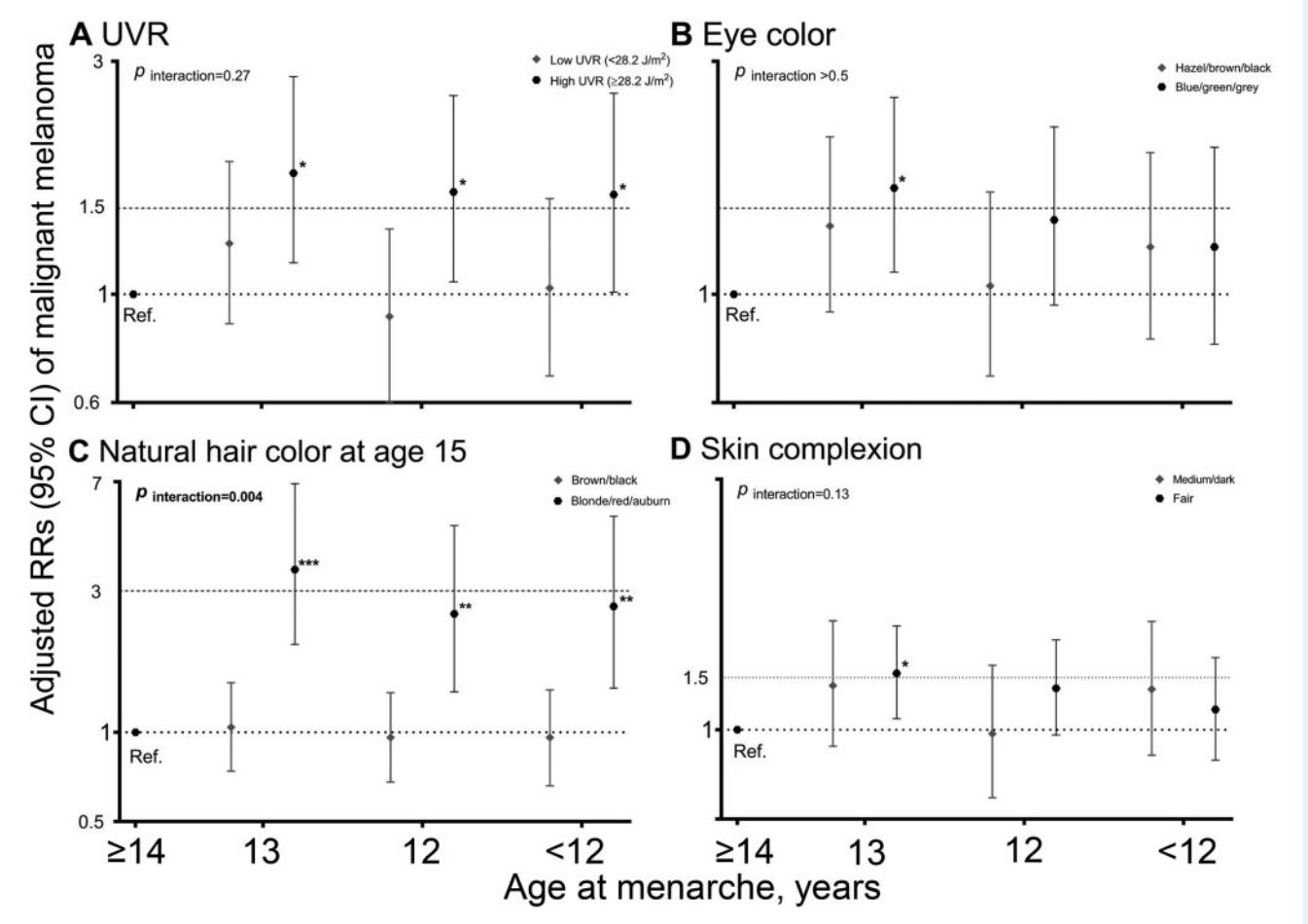

Figure 1. The risks of malignant melanoma for age at menarche among 46 544 women in the US Radiologic Technologists Study by (A) ultraviolet radiation (UVR); (B) eye color; (C) natural hair color at age 15 and (D) skin complexion. Adjusted for age, birth cohort (1905–1940, 1941–1945, 1946–1950, 1951–1955, 1956–1966), lifetime average annual ambient UVR (Quartile 1–4), and oral contraceptives use (never, ever) as appropriate. Trend tests were conducted by modeling categorical values as ordinal, and all *P*-values for trend were >0.05. Likelihood-ratio test for multiplicative interaction of average lifetime annual erythemal UVR in the associations between age at menarche and melanoma, and all *P*-values for interaction were >0.05; except natural hair color at age 15 with bold indicating statistically significant (*P*-value for interaction = 0.004). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. RR, risk ratio; Ref, reference.

from adulthood (e.g. age at first live birth) (Bosetti *et al.*, 2001). We did not have information on specific doses or formulations of exogenous hormone medications or breastfeeding. While we adjusted for previously reported predictors of more frequent skin cancer and medical and self-screening (older age, living with partner(s), light hair color and fair skin complexion), the possibility of melanoma detection bias cannot be ruled out (McPherson *et al.*, 2006; Goldberg *et al.*, 2007; Curiel-Lewandrowski *et al.*, 2012). Generalizability might be a concern because the present analysis included non-Hispanic white females only, and our USRT participants are medical workers who are likely to have high overall health care utilization patterns with potentially less variability than the general population. The number of participants with melanoma was relatively small in the current prospective cohort study with detailed information on confounders of melanoma, lifetime ambient UVR exposure, and personal sun sensitivity. We did not correct for multiple testing, so the role of chance must be considered in the interpretation of our findings.

Conclusions

Earlier age at menarche and late age at first birth were associated with higher incidence rates of melanoma in this large, geographically dispersed cohort of non-Hispanic white female radiologic technologists. Women residing in areas of high ambient UVR and those with blonde/red/auburn natural hair color may constitute an additional high-risk group in need of more frequent skin cancer screening. Future larger studies could collect more detailed information on photosensitizing medication use and breastfeeding, and ideally, estimates of genetically predicted levels of estrogen, particularly for childhood. Identifying susceptible periods of exposure or factors that modify UVR susceptibility may aid in guiding more targeted guidelines for melanoma prevention.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request or the principal investigator of the US Radiologic Technologists study (Dr Cari M. Kitahara).

Authors' roles

J.Z.M. and E.K.C. designed and initiated the study. B.H.A. and C.M.K. were responsible for acquisition of data. J.Z.M., R.Z. and E.K.C. produced an analytical plan. J.Z.M. and R.Z. were responsible for data analysis. J.Z.M. produced a first draft of the manuscript. J.Z.M. and E.K.C. are guarantors. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript.

Funding

This research was supported by the Intramural Research Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services.

Conflict of interest

The authors declare no potential conflicts of interest.

References

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.

Armstrong BK, Vajdic CM, Cust AE. Melanoma. In: Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D (eds). *Cancer Epidemiology and Prevention*. Oxford: Oxford University Press, 2017, 1061–1088.

Bosetti C, Tavani A, Negri E, Trichopoulos D, La Vecchia C. Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. *J Clin Epidemiol* 2001;**54**: 902–906.

Botteri E, Støer NC, Sakshaug S, Graff-Iversen S, Vangen S, Hofvind S, Ursin G, Weiderpass E. Menopausal hormone therapy and risk of melanoma: do estrogens and progestins have a different role? *Int J Cancer* 2017;**141**:1763–1770.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**:394–424.

Cervenka I, Al Rahmoun M, Mahamat-Saleh Y, Fournier A, Boutron-Ruault M-C, Severi G, Caini S, Palli D, Ghiasvand R, Veierod MB *et al.* Exogenous hormone use and cutaneous melanoma risk in women: the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2020;**146**:3267–3280.

Cervenka I, Al Rahmoun M, Mahamat-Saleh Y, Savoye I, Boutron-Ruault M, Fournier A, Kvaskoff M. Postmenopausal hormone use and cutaneous melanoma risk: a French prospective cohort study. *Int J Cancer* 2019;**145**:1754–1767.

Cervenka I, Mahamat-Saleh Y, Savoye I, Dartois L, Boutron-Ruault M, Fournier A, Kvaskoff M. Oral contraceptive use and cutaneous melanoma risk: a French prospective cohort study. *Int J Cancer* 2018;**143**:2390–2399.

Chavez-MacGregor M, Elias SG, Onland-Moret NC, Van Der Schouw YT, Van Gils CH, Monninkhof E, Grobbee DE, Peeters PH. Postmenopausal breast cancer risk and cumulative number of menstrual cycles. *Cancer Epidemiol Biomarkers Prev* 2005;**14**: 799–804.

Choi K, Lazovich D, Southwell B, Forster J, Rolnick SJ, Jackson J. Prevalence and characteristics of indoor tanning use among men

and women in the United States. *Arch Dermatol* 2010;**146**:1356–1361.

Cooper R, Blell M, Hardy R, Black S, Pollard T, Wadsworth M, Pearce M, Kuh D. Validity of age at menarche self-reported in adulthood. *J Epidemiol Community Health* 2006;**60**:993–997.

Curiel-Lewandrowski C, Chen SC, Swetter SM; Melanoma Prevention Working Group-Pigmented Skin Lesion Sub-Committee. Screening and prevention measures for melanoma: is there a survival advantage? *Curr Oncol Rep* 2012;**14**:458–467.

Donley GM, Liu WT, Pfeiffer RM, McDonald EC, Peters KO, Tucker MA, Cahoon EK. Reproductive factors, exogenous hormone use and incidence of melanoma among women in the United States. *Br J Cancer* 2019;**120**:754–760.

Eilers S, Bach DQ, Gaber R, Blatt H, Guevara Y, Nitsche K, Kundu RV, Robinson JK. Accuracy of self-report in assessing Fitzpatrick skin phototypes I through VI. *JAMA Dermatol* 2013;**149**:1289–1294.

Freedman DM, Sigurdson A, Rao RS, Hauptmann M, Alexander B, Mohan A, Doody MM, Linet MS. Risk of melanoma among radiologic technologists in the United States. *Int J Cancer* 2003;**103**:556–562.

Freedman DM, Sigurdson AJ, Doody MM, Love-Schnur S, Linet MS. Comparison between cancers identified by state cancer registry, self-report, and death certificate in a prospective cohort study of US radiologic technologists. *Int J Epidemiol* 2006;**35**:495–497.

Fuhrman BJ, Moore SC, Byrne C, Makhoul I, Kitahara CM, Berrington de González A, Linet MS, Weiderpass E, Adami H-O, Freedman ND *et al.* Association of the age at Menarche with site-specific cancer risks in pooled data from nine cohorts. *Cancer Res* 2021;**81**:2246–2255.

Gandini S, Iodice S, Koomen E, Di Pietro A, Sera F, Caini S. Hormonal and reproductive factors in relation to melanoma in women: current review and meta-analysis. *Eur J Cancer* 2011;**47**:2607–2617.

Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, Melchi CF. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer* 2005;**41**:45–60.

Goldberg MS, Doucette JT, Lim HW, Spencer J, Carucci JA, Rigel DS. Risk factors for presumptive melanoma in skin cancer screening: American Academy of Dermatology National Melanoma/Skin Cancer Screening Program experience 2001-2005. *J Am Acad Dermatol* 2007;**57**:60–66.

Henley SJ, Ward EM, Scott S, Ma J, Anderson RN, Firth AU, Thomas CC, Islami F, Weir HK, Lewis DR *et al.* Annual report to the nation on the status of cancer, Part I: National cancer statistics. *Cancer* 2020;**126**:2225–2249.

Kaae J, Andersen A, Boyd HA, Wohlfahrt J, Melbye M. Reproductive history and cutaneous malignant melanoma: a comparison between women and men. *Am J Epidemiol* 2007;**165**:1265–1270.

Kitahara CM, Preston DL, Neta G, Little MP, Doody MM, Simon SL, Sigurdson AJ, Alexander BH, Linet MS. Occupational radiation exposure and thyroid cancer incidence in a cohort of US radiologic technologists, 1983–2013. *Int J Cancer* 2018;**143**:2145–2149.

Kvaskoff M, Bijon A, Mesrine S, Boutron-Ruault M-C, Clavel-Chapelon F. Cutaneous melanoma and endogenous hormonal factors: a large French prospective study. *Am J Epidemiol* 2011;**173**:1192–1202.

Liu F, Bessonova L, Taylor TH, Ziogas A, Meyskens FL, Anton-Culver H. A unique gender difference in early onset melanoma implies that in addition to ultraviolet light exposure other causative factors are important. *Pigment Cell Melanoma Res* 2013;**26**:128–135.

Liu JJ, Freedman DM, Little MP, Doody MM, Alexander BH, Kitahara CM, Lee T, Rajaraman P, Miller JS, Kampa DM *et al.* Work history and mortality risks in 90 268 US radiological technologists. *Occup Environ Med* 2014;**71**:819–835.

Lundblad MW, Jacobsen BK. The reproducibility of self-reported age at menarche: the Tromsø Study. *BMC Women's Health* 2017;**17**:1–7.

McPherson M, Elwood M, English DR, Baade PD, Youl PH, Aitken JF. Presentation and detection of invasive melanoma in a high-risk population. *J Am Acad Dermatol* 2006;**54**:783–792.

Olsen C, Pandeya N, Dusingize J, Thompson B, Green A, Neale R, Webb P, Whiteman D, QSkin Study. Reproductive factors, hormone use and melanoma risk: an Australian prospective cohort study. *Br J Dermatol* 2021;**184**:361–363.

Olsen CM, Thompson JF, Pandeya N, Whiteman DC. Evaluation of sex-specific incidence of melanoma. *JAMA Dermatol* 2020;**156**:553–560.

Reeder AI, Hammond VA, Gray AR. Questionnaire items to assess skin color and erythemal sensitivity: reliability, validity, and "the dark shift". *Cancer Epidemiol Biomarkers Prev* 2010;**19**:1167–1173.

Richarz N, Aguilera J, Castillo G, Fuente M, Ferrándiz C, Carrascosa J. Phototoxic reaction to a combined oral contraceptive (levonorgestrel/ethinylestradiol). *Photochem Photobiol Sci* 2017;**16**:1381–1383.

Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990;**1**:43–46.

Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA A Cancer J Clin* 2021;**71**:7–33.

Sigurdson AJ, Doody MM, Rao RS, Freedman DM, Alexander BH, Hauptmann M, Mohan AK, Yoshinaga S, Hill DA, Tarone R *et al.* Cancer incidence in the US radiologic technologists health study, 1983–1998. *Cancer* 2003;**97**:3080–3089.

Stern RS. Photocarcinogenicity of drugs. *Toxicol Lett* 1998;**102–103**:389–392.

Sun Q, Sun H, Cong L, Zheng Y, Wu N, Cong X. Effects of exogenous hormones and reproductive factors on female melanoma: a meta-analysis. *Clin Epidemiol* 2020;**12**:1183–1203.

Tang JY, Spaunhurst KM, Chlebowski RT, Wactawski-Wende J, Keiser E, Thomas F, Anderson ML, Zeitouni NC, Larson JC, Stefanick ML. Menopausal hormone therapy and risks of melanoma and nonmelanoma skin cancers: women's health initiative randomized trials. *J Natl Cancer Inst* 2011;**103**:1469–1475.

Tang X, Zhang H, Cui Y, Wang L, Wang Z, Zhang Y, Huo J, Cai J, Rinaldi G, Bhagavathula AS *et al.* Postmenopausal exogenous hormone therapy and melanoma risk in women: a systematic review and time-response meta-analysis. *Pharmacol Res* 2020;**160**:105182.

Thrift AP, Gudenkauf FJ. Melanoma incidence among Non-Hispanic Whites in all 50 US states from 2001 through 2015. *J Natl Cancer Inst* 2020;**112**:533–539.

Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. *Cancer Causes Control* 2001;**12**:69–82.

Wu S, Han J, Laden F, Qureshi AA. Long-term ultraviolet flux, other potential risk factors, and skin cancer risk: a cohort study. *Cancer Epidemiol Biomarkers Prev* 2014;**23**:1080–1089.