International Journal of Epidemiology, 2014, 1–9
doi: 10.1093/ije/dyt277
Original article

Original article

Season of birth and other perinatal risk factors for melanoma

Casey Crump,[1]* Kristina Sundquist,[2,3] Weiva Sieh,[4] Marilyn A Winkleby[3] and Jan Sundquist[2,3]

[1]Department of Medicine, Stanford University, Stanford, CA, USA, [2]Center for Primary Health Care Research, Lund University, Malmö, Sweden, [3]Stanford Prevention Research Center, Stanford University, Stanford, CA, USA and [4]Department of Health Research and Policy, Stanford University, Stanford, CA, USA

*Corresponding author. Stanford University, Department of Medicine, 211 Quarry Road, Suite 405, MC 5985, Palo Alto, CA, USA. E-mail: kccrump@stanford.edu

Accepted 17 December 2013

Abstract

Background: Ultraviolet radiation (UVR) exposure is the main risk factor for cutaneous malignant melanoma (CMM), but its specific effect in infancy is unknown. We examined whether season of birth, a proxy for solar UVR exposure in the first few months of life, is associated with CMM in childhood through young adulthood.

Methods: National cohort study of 3 571 574 persons born in Sweden in 1973–2008, followed up for CMM incidence through 2009 (maximum age 37 years) to examine season of birth and other perinatal factors.

Results: There were 1595 CMM cases in 63.9 million person-years of follow-up. We found a sinusoidal pattern in CMM risk by season of birth ($P = 0.006$), with peak risk corresponding to birthdates in spring (March–May). Adjusted odds ratios for CMM by season of birth were 1.21 [95% confidence interval (CI), 1.05–1.39; $P = 0.008$] for spring, 1.07 (95% CI, 0.92–1.24; $P = 0.40$) for summer and 1.12 (95% CI, 0.96–1.29; $P = 0.14$) for winter, relative to fall. Spring birth was associated with superficial spreading subtype of CMM ($P = 0.02$), whereas there was no seasonal association with nodular subtype ($P = 0.26$). Other CMM risk factors included family history of CMM in a sibling (>6-fold) or parent (>3-fold), female gender, high fetal growth and high paternal education level.

Conclusions: In this large cohort study, persons born in spring had increased risk of CMM in childhood through young adulthood, suggesting that the first few months of life may be a critical period of UVR susceptibility. Sun avoidance in early infancy may play an important role in the prevention of CMM in high-risk populations.

Key words: fetal development, melanoma, risk factors, seasons

Key Messages

- In this Swedish national cohort study, we found a sinusoidal pattern in risk of cutaneous malignant melanoma (CMM) by season of birth, with peak risk corresponding to birthdates in spring (March–May).
- Other CMM risk factors included family history of CMM, female gender, high fetal growth, and high paternal education level.
- The observed association between spring birth and CMM suggests that the first few months of life may be a critical period of susceptibility to solar UVR exposures. Sun avoidance in early infancy may play an important role in the prevention of CMM in high-risk populations.

Introduction

The incidence of cutaneous malignant melanoma (CMM) has increased in Western countries over the past five decades.[1] Although ultraviolet radiation (UVR) exposure is the main risk factor, the effect of UVR exposure during infancy on CMM risk in later life is unknown. Previous studies have reported that childhood sun exposures are a strong determinant of CMM risk in later life but have not specifically examined exposures in infancy.[2,3] Recent evidence that UVR-related pigmentation begins in the first summer of life[4] has suggested that solar UVR exposures in infancy may play an important role in the development of CMM, particularly in susceptible populations that lack the protective effect of high skin melanin concentration.[5,6] Direct assessment of UVR exposures on the individual level is usually not feasible in cohorts that are sufficiently large to test this hypothesis. However, season of birth is a useful proxy for solar UVR exposures in the first few months of life. We hypothesized that persons born in Sweden just prior to summer, preceding the period of highest solar UVR exposures, would have an increased risk of CMM in later life (note that the opposite seasonal pattern would be expected in the Southern Hemisphere). If confirmed, this would suggest that the first few months of life are an important period of UVR susceptibility, and would help target preventive interventions.

In addition to UVR exposure and genetic susceptibility,[7] other perinatal and familial risk factors for CMM have also been hypothesized, including high birthweight,[8,9] older parental age[8,10] and early birth order.[8,11,12] Previous studies of these putative risk factors have yielded mixed results, due in part to differences in study design or sample selection, and insufficient sample sizes. Large population-based cohort studies have the potential to clarify these risk factors and improve the understanding of mechanisms involved in the development of CMM. We conducted a national cohort study of 3.5 million people in Sweden to examine whether season of birth and other perinatal and familial factors are associated with CMM in childhood through young adulthood.

Methods

Study population

We identified 3 595 055 individuals in the Swedish Birth Registry who were born from 1973 through 2008. Month and day of birth information was complete for the entire cohort. We excluded 10 438 (0.3%) individuals who had missing information for birthweight, and 7704 (0.2%) others who had missing information for gestational age at birth. To remove possible coding errors, we also excluded 5339 (0.1%) others who had a reported birthweight more than four standard deviations (SD) above or below the mean birthweight for gestational age and gender based on a Swedish reference growth curve.[13] A total of 3 571 574 individuals (99.3% of the original cohort) remained for inclusion in the study. This study was approved by the Regional Ethics Committee of Lund University in Sweden.

Melanoma ascertainment

The study cohort was followed for CMM incidence from birth through 31 December 2009 (maximum attained age was 37 years). All incident CMM cases were identified using the International Classification of Diseases, 7th revision, code 190, in the Swedish Cancer Registry. This registry includes all primary incident cancers in Sweden since 1958, with compulsory reporting nationwide. CMM subtypes that were sufficiently common for separate analysis were identified using standard ICD-O codes (8743 for superficial spreading melanoma and 8721 for nodular melanoma). Information on Breslow's thickness (a prognostic indicator for melanoma) was unavailable.

Perinatal and familial variables

Perinatal and familial characteristics that may be associated with CMM were identified from the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number.[14] The following variables were examined as predictors of interest or

adjustment variables: gender; birth year [modelled simultaneously as continuous and categorical (1973–79, 1980–84, 1985–89, 1990–2008) variables to allow for a non-linear effect]; season of birth (modelled as a sinusoidal function, as described below); fetal growth [a standardized fetal growth variable defined as the number of standard deviations from the mean birthweight for gestational age and gender based on a Swedish reference growth curve,[13] modelled alternatively as a categorical (<-2; −2 to <-1; −1 to <0; 0 to <1; 1 to <2; ≥2 SD) or continuous variable]; gestational age at birth [based primarily on maternal report of last menstrual period in the 1970s, at which time ultrasound estimation was gradually introduced until it was used exclusively starting in the 1990s; modeled alternatively as a categorical (<37, 37–42, ≥43 weeks) or continuous variable]; birthweight [modelled alternatively as a categorical (<2500, 2500–3999, ≥4000 g) or continuous variable]; birth length [crown-heel length in cm, modelled alternatively as a categorical (<48, 48_52, ≥53 cm) or continuous variable]; multiple birth (singleton vs twin or higher order); birth order (1, 2, 3, 4, ≥5); maternal and paternal age at birth (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years; examined separately for mothers and fathers); parental country of birth (both parents born in Sweden, both born in Europe/USA/Canada but not both in Sweden, one or both born in other countries; note that other specific information on ethnicity was unavailable); maternal and paternal education level [compulsory high school or less (≤9 years), practical high school or some theoretical high school (10–11 years), theoretical high school and/or some college (12–14 years), college and/or postgraduate study (≥15 years); examined separately for mothers and fathers]; and family history of CMM in a parent or sibling (yes or no; identified from the Swedish Cancer Registry from 1958 through 2009, not self-reported, thus enabling highly complete and unbiased ascertainment during this time period, and examined separately for parents and siblings).

Statistical analysis

We explored different statistical models to identify the best fit to the data. Logistic regression was a good fit in all models using the Pearson chi-square or Hosmer–Lemeshow tests.[15] In contrast, Poisson regression violated goodness-of-fit tests in all models; and Cox proportional hazards regression was a poor fit in most models, whereas it gave essentially identical results as logistic regression in others in which the proportional hazards assumption was satisfied. As a result, logistic regression was used in the final models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between the predictor variables and CMM.

Season of birth was modelled using standard methods for seasonal data. First, date of birth (DOB, coded as an integer from 1 to 365) was modelled as a sinusoidal function in the logistic regression model, using an iterative method to identify the peak date for CMM relative risk and to test for an overall seasonal association, as previously described.[16] In the case of a leap year, February 29 was recoded as calendar day 59 so that the respective year had 365 days. Specifically, the trigonometric term entered into the logistic model was:

$$x = \cos[2 \times \arccos(-1) \times ((\mathrm{DOB} - t_{max})/365)]$$

where t_{max} (the peak birth date for CMM risk) was determined iteratively by finding the value from 1 to 365 that maximized the model coefficient.[16] After identifying the peak date in this manner, the 3-month period of maximum risk was identified by centring on this date.

Two different adjusted models were used. The first was adjusted for birth year, and the second was further adjusted for other variables that were found to be associated with CMM (gender, season of birth, parental country of birth, paternal education level, and family history of CMM in a parent or sibling). First-order interactions between gender or season of birth and other variables were explored using a likelihood ratio test. In addition, multinomial logistic regression was used to test for heterogeneity in the association between each risk factor and earlier-onset (age <15 years) vs later-onset (age ≥15 years) CMM. We also repeated the same models described above to explore associations between perinatal or familial variables and the most common CMM subtypes (superficial spreading and nodular melanoma). All statistical tests were 2-sided and used an α-level of 0.05. All analyses were conducted using Stata version 13.0.[17]

Results

Among the 3 571 574 persons in this cohort, 1595 CMM cases were identified in 63.9 million person-years of follow-up. The mean age at CMM diagnosis was 26.3 years (SD 5.6, median 26.8, range 1.4 to 36.8 years). CMM incidence by season or month of birth is shown in Table 1, and was highest among persons born in April or May (2.79 and 2.82 cases per 100 000 person-years, respectively). In the logistic model, we found a sinusoidal pattern in CMM risk by season of birth ($P = 0.006$, adjusted for birth year), with peak risk corresponding to a birth date of 13 April and lowest risk corresponding to a birth date of 12 October. Figure 1 shows the seasonal pattern in relative risk of CMM from the sinusoidal model. The 3-month period of maximum risk, identified by centring around the peak

Table 1. Incidence of cutaneous malignant melanoma (CMM) 1973–2009 by season or month of birth

Season	Births	Person-years	CMM cases	
	No. (%)	(millions)	No. (%)	No. per 100 000 person-years
Overall	3 571 574 (100.0)	63.95	1 595 (100.0)	2.49
Spring	990 773 (27.7)	18.17	498 (31.2)	2.74
March	334 787 (9.4)	6.20	162 (10.2)	2.61
April	331 520 (9.3)	6.09	170 (10.7)	2.79
May	324 466 (9.1)	5.88	166 (10.4)	2.82
Summer	915 888 (25.6)	16.15	384 (24.1)	2.38
June	305 267 (8.6)	5.45	127 (8.0)	2.33
July	310 043 (8.7)	5.44	131 (8.2)	2.41
August	300 578 (8.4)	5.26	126 (7.9)	2.40
Fall	822 327 (23.0)	14.38	330 (20.7)	2.29
September	291 196 (8.2)	5.13	116 (7.3)	2.26
October	278 533 (7.8)	4.84	115 (7.2)	2.37
November	252 598 (7.1)	4.41	99 (6.2)	2.25
Winter	842 586 (23.6)	15.25	383 (24.0)	2.51
December	253 596 (7.1)	4.42	100 (6.3)	2.26
January	297 241 (8.3)	5.47	144 (9.0)	2.63
February	291 749 (8.2)	5.36	139 (8.7)	2.59

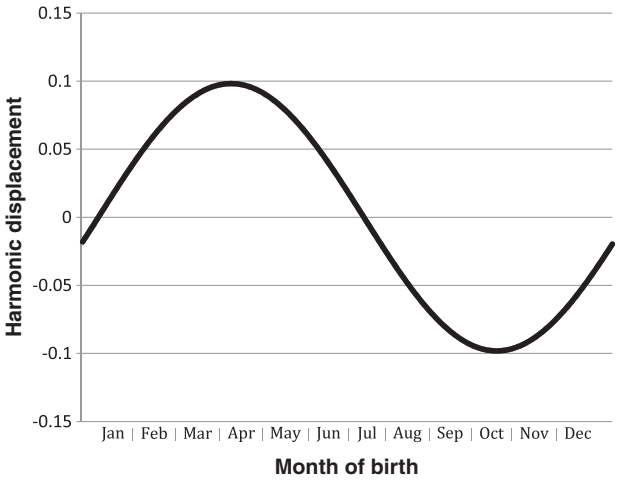

Figure 1. Sinusoidal logistic regression results for association between birth date and cutaneous malignant melanoma in childhood through young adulthood, adjusted for birth year ($P = 0.006$ for overall seasonal association). Harmonic displacement represents the log odds ratio for a given time point relative to the mean risk across the entire calendar year.

date (13 April), coincided nearly exactly with March through May, and the 3-month period of minimum risk with September through November. As a result, season of birth was examined in subsequent models as spring (March–May), summer (June–August) or winter (December–February), relative to fall (September–November).

Unadjusted ORs for CMM by season of birth were 1.25 (95% CI, 1.09–1.44; $P = 0.002$) for spring, 1.04 (95% CI, 0.90–1.21; $P = 0.56$) for summer and 1.13 (95% CI, 0.98–1.31; $P = 0.10$) for winter, relative to fall (not shown in the tables). The distribution of season of birth varied comparing earlier with later birth cohorts, hence birth year was considered as a potential confounder. After adjusting for birth year (Table 2, adjusted model 1), ORs for CMM by season of birth were 1.22 (95% CI, 1.06-1.40; $P = 0.005$) for spring, 1.07 (95% CI, 0.92-1.24; $P = 0.38$) for summer and 1.12 (95% CI, 0.96-1.30; $P = 0.13$) for winter, relative to fall. Further adjustment for other variables had a negligible effect on these risk estimates (Table 2, adjusted model 2). For spring relative to fall birth, the fully adjusted OR for early-onset CMM (age <15 years) was 2.13 (95% CI, 0.89-5.11; P = 0.09; based on 42 cases) and for later-onset CMM (≥15 years) was 1.19 (95% CI, 1.03-1.37; P = 0.02; based on 1553 cases) (test for heterogeneity between aORs, $P = 0.19$; not shown in the tables).

The strongest overall risk factors for CMM were a family history of CMM in a sibling or parent (>6-fold and >3-fold risks, respectively; Table 2, adjusted model 2). A parental history of CMM appeared to be more strongly associated with earlier-onset CMM (age <15 years, aOR, 8.27; 95% CI, 2.91-23.44; $P < 0.001$; based on 42 cases) compared with later-onset CMM (age ≥15 years, aOR, 3.12; 95% CI, 2.41-3.90; $P < 0.001$) (test for heterogeneity between aORs, $P = 0.07$; not shown in the tables). There was no heterogeneity in the association between CMM in a sibling and earlier-onset (<15 years) vs later-onset (≥15 years) CMM in the proband. We also found no evidence that the association between family history and CMM varied by whether the affected family member was male or

Table 2. Adjusted odds ratios for associations between perinatal or familial characteristics and cutaneous malignant melanoma (CMM) 1973–2009

Characteristic	Total population	CMM cases	Adjusted model 1[a]			Adjusted model 2[b]		
	No. (%)	No. (%)	OR	95% CI	*P*	OR	95% CI	*P*
Age at diagnosis (years)								
<5		4 (0.3)						
5–9		6 (0.4)						
10–14		32 (2.0)						
15–19		181 (11.4)						
20–24		395 (24.8)						
25–29		505 (31.7)						
≥30		472 (29.6)						
Gender								
Male	1 835 588 (51.4)	553 (34.7)	1.00			1.00		
Female	1 735 986 (48.6)	1 042 (65.3)	2.00	1.80, 2.21	<0.001	2.00	1.80, 2.21	<0.001
Season of birth								
Spring (Mar–May)	990 773 (27.7)	498 (31.2)	1.22	1.06, 1.40	0.005	1.21	1.05, 1.39	0.008
Summer (Jun–Aug)	915 888 (25.6)	384 (24.1)	1.07	0.92, 1.24	0.38	1.07	0.92, 1.24	0.40
Fall (Sep–Nov)	822 327 (23.0)	330 (20.7)	1.00			1.00		
Winter (Dec–Feb)	842 586 (23.6)	383 (24.0)	1.12	0.97, 1.30	0.13	1.12	0.96, 1.29	0.14
Fetal growth (SDs)								
<-2	112 440 (3.1)	57 (3.6)	0.69	0.52, 0.91		0.70	0.53, 0.93	
-2 to <-1	535 817 (15.0)	291 (18.2)	0.93	0.81, 1.08		0.93	0.81, 1.08	
-1 to <0	1 266 800 (35.5)	542 (34.0)	0.87	0.77, 0.98		0.87	0.77, 0.98	
0 to <1	1 118 797 (31.3)	493 (30.9)	1.00			1.00		
1 to <2	428 757 (12.0)	162 (10.2)	0.92	0.77, 1.10		0.93	0.77, 1.11	
≥2	108 963 (3.1)	50 (3.1)	1.16	0.87, 1.55		1.17	0.87, 1.56	
Per SD (trend test)			1.06	1.01, 1.10	0.02	1.06	1.01, 1.10	0.02
Gestational age at birth (weeks)								
<37	206 835 (5.8)	71 (4.5)	0.84	0.66, 1.07		0.89	0.70, 1.13	
37-42	3 323 840 (93.1)	1 488 (93.3)	1.00			1.00		
≥43	40 899 (1.1)	36 (2.3)	0.88	0.63, 1.22		0.88	0.63, 1.22	
Per week (trend test)			1.03	1.01, 1.06	0.02	1.02	1.00, 1.05	0.09
Birthweight (g)								
<2500	149 359 (4.2)	52 (3.3)	0.81	0.61, 1.07		0.82	0.62, 1.09	
2500–3999	2 779 681 (77.8)	1 265 (79.3)	1.00			1.00		
≥4000	642 534 (18.0)	278 (17.4)	1.07	0.94, 1.22		1.15	1.01, 1.31	
Per 1000 g (trend test)			1.12	1.03, 1.23	0.01	1.18	1.08, 1.29	<0.001
Birth length (cm)								
<48	359 988 (10.1)	138 (8.7)	0.88	0.74, 1.05		0.86	0.72, 1.03	
48–52	2 601 357 (72.8)	1 199 (75.2)	1.00			1.00		
≥53	577 004 (16.2)	255 (16.0)	0.96	0.84, 1.10		1.09	0.95, 1.25	
Unknown	33 225 (0.9)	3 (0.2)	0.45	0.15, 1.40		0.49	0.16, 1.53	
Per cm (trend test)			1.01	0.99, 1.03	0.30	1.03	1.01, 1.05	0.006
Multiple birth								
Singleton	3 487 043 (97.6)	1 569 (98.4)	1.00			1.00		
Twin or higher order	84 474 (2.4)	26 (1.6)	0.93	0.63, 1.38	0.73	0.92	0.63, 1.36	0.69
Birth order								
1	1 411 435 (39.5)	691 (43.3)	1.00			1.00		
2	1 224 253 (34.3)	618 (38.7)	1.04	0.93, 1.16		1.02	0.91, 1.14	
3	509 759 (14.3)	223 (14.0)	0.97	0.83, 1.13		0.95	0.82, 1.11	
4	148 413 (4.2)	48 (3.0)	0.79	0.59, 1.06		0.80	0.60, 1.07	
≥5	67 533 (1.9)	15 (0.9)	0.59	0.36, 0.99		0.64	0.38, 1.06	
Unknown	210 181 (5.9)	0 (0.0)	NE	NE		NE	NE	
Per each higher category (trend test)			0.95	0.90, 1.01	0.09	0.95	0.90, 1.00	0.07

(Continued)

Table 2. (Continued)

Characteristic	Total population	CMM cases	Adjusted model 1[a]			Adjusted model 2[b]		
	No. (%)	No. (%)	OR	95% CI	*P*	OR	95% CI	*P*
Maternal age at birth (years)								
<20	84 008 (2.3)	67 (4.2)	0.91	0.71, 1.17		1.02	0.79, 1.32	
20–24	678 209 (19.0)	375 (23.5)	0.82	0.73, 0.94		0.87	0.77, 0.99	
25–29	1 251 782 (35.1)	654 (41.0)	1.00			1.00		
30–34	1 034 457 (29.0)	375 (23.5)	0.98	0.86, 1.11		0.96	0.85, 1.09	
35–40	432 425 (12.1)	107 (6.7)	0.87	0.71, 1.07		0.86	0.70, 1.06	
≥40	86 575 (2.4)	17 (1.1)	0.82	0.51, 1.33		0.84	0.52, 1.36	
Unknown	4118 (0.1)	0 (0.0)	NE	NE		NE	NE	
Per each higher category (trend test)			1.03	0.98, 1.08	0.25	1.00	0.95, 1.05	0.98
Paternal age at birth (years)								
<20	16 949 (0.5)	9 (0.6)	0.80	0.41, 1.54		0.92	0.47, 1.78	
20–24	327 052 (9.2)	209 (13.1)	0.96	0.82, 1.12		1.01	0.86, 1.18	
25–29	1 021 995 (28.6)	569 (35.7)	1.00			1.00		
30–34	1 161 825 (32.5)	517 (32.4)	1.10	0.97, 1.24		1.07	0.95, 1.21	
35–40	657 548 (18.4)	192 (12.0)	0.97	0.82, 1.14		0.96	0.81, 1.13	
≥40	357 578 (10.0)	88 (5.5)	0.92	0.73, 1.15		0.93	0.74, 1.17	
Unknown	28 627 (0.8)	11 (0.7)	0.88	0.49, 1.61		1.30	0.67, 2.50	
Per each higher category (trend test)			1.01	0.96, 1.05	0.79	0.99	0.95, 1.04	0.75
Parental country of birth								
Both born in Sweden	2 854 201 (79.9)	1 416 (88.8)	1.00			1.00		
Both born in Europe/USA/Canada (but not both Sweden)	417 438 (11.7)	164 (10.3)	0.71	0.60, 0.83	<0.001	0.76	0.65, 0.90	0.001
1 or both born in other countries	299 901 (8.4)	15 (0.9)	0.34	0.20, 0.57	<0.001	0.37	0.22, 0.62	<0.001
Maternal education (years)								
≤9	675 199 (18.9)	474 (29.7)	1.00			1.00		
10–11	1 150 381 (32.2)	542 (34.0)	0.92	0.81, 1.04		0.90	0.80, 1.02	
12–14	1 045 489 (29.3)	329 (20.6)	1.02	0.89, 1.18		0.95	0.82, 1.10	
≥15	554 895 (15.5)	200 (12.5)	1.09	0.92, 1.29		0.98	0.81, 1.19	
Unknown	145 610 (4.1)	50 (3.1)	0.54	0.40, 0.72		0.60	0.45, 0.81	
Per each higher category (trend test)			1.03	0.98, 1.08	0.25	0.99	0.93, 1.05	0.73
Paternal education (years)								
≤9	767 733 (21.5)	495 (31.0)	1.00			1.00		
10–11	1 129 269 (31.6)	399 (25.0)	0.94	0.83, 1.08		0.94	0.83, 1.08	
12–14	960 319 (26.9)	400 (25.1)	1.15	1.01, 1.32		1.14	1.00, 1.30	
≥15	538 137 (15.1)	237 (14.9)	1.15	0.98, 1.34		1.12	0.96, 1.31	
Unknown	176 116 (4.9)	64 (4.0)	0.64	0.49, 0.82		0.76	0.58, 0.99	
Per each higher category (trend test)			1.06	1.01, 1.12	0.01	1.05	1.01, 1.11	0.03
CMM in a parent								
No	3 535 454 (99.0)	1 510 (94.7)	1.00			1.00		
Yes	36 120 (1.0)	85 (5.3)	3.39	2.73, 4.23	<0.001	3.21	2.58, 4.00	<0.001
CMM in a sibling								
No	3 569 772 (99.9)	1 583 (99.2)	1.00			1.00		
Yes	1802 (<0.1)	12 (0.8)	7.39	4.18, 13.08	<0.001	6.53	3.68, 11.58	<0.001

The reference category for all variables is indicated by an odds ratio of 1.00. Missing data were excluded for trend tests.

NE, not estimable.

[a]Adjusted for birth year (modelled simultaneously as continuous and categorical variables).

[b]Adjusted for birth year (as noted above), gender, season of birth, parental country of birth, paternal education and family history of CMM in a parent or sibling.

female ($P = 0.86$), or by whether the affected family member was the same or opposite sex as the proband ($P = 0.19$).

Other risk factors for CMM in the fully adjusted model included female gender (2-fold risk relative to males), high fetal growth ($P_{trend} = 0.02$), high birthweight ($P_{trend} < 0.001$), high birth length ($P_{trend} = 0.006$) and high paternal education level ($P_{trend} = 0.03$) (Table 2, adjusted model 2). Risk of CMM also was lower among those who had one or both parents born outside Sweden (and especially with a parent born outside Europe, USA or Canada), relative to those whose parents were both Swedish-born (Table 2). Only 3317 (<0.1%) persons (and only 1 with CMM) had a parent who was born in Australia or New Zealand, which precluded separate analysis of this group.

High gestational age at birth was associated with CMM before but not after adjusting for covariates in the fully adjusted model (Table 2). A modest trend of decreasing CMM risk by later birth order was also noted ($P_{trend} = 0.07$; Table 2, adjusted model 2). Multiple birth, maternal and paternal age and maternal education level were not associated with CMM.

We found no interactions between gender or season of birth and any other variables with respect to CMM risk, including none directly between gender and season of birth ($P = 0.09$). Also, with the possible exceptions of season of birth and parental history of CMM (as noted above), there was no evidence of heterogeneity in the association between any other variable and earlier-onset (<15 years) vs later-onset (≥15 years) CMM.

CMM subtype information was available for 864 (54.2%) cases. The most common subtypes were superficial spreading ($n = 744$) and nodular ($n = 89$) melanoma, whereas there were too few cases of lentigo maligna melanoma ($n = 18$) or other known subtypes ($n = 13$) for meaningful analysis. A sinusoidal pattern in the risk of superficial spreading subtype was found by season of birth ($P = 0.02$, adjusted for birth year), with peak risk corresponding to a birth date of 20 April. For spring relative to fall birth, the fully adjusted OR for superficial spreading subtype was 1.24 (95% CI, 1.01-1.52; $P = 0.04$). Other risk factors for superficial spreading subtype were consistent with the overall CMM findings except that the associations with fetal growth and paternal education were attenuated, although the trends were in the same direction (see eTable 1 for full results, available as Supplementary data at *IJE* online). In contrast, there was no clear sinusoidal pattern in the risk of nodular subtype by season of birth ($P = 0.26$, adjusted for birth year). Other results for nodular subtype differed from those for CMM overall or superficial spreading subtype in that there was no increased risk among females, nor a positive trend by higher paternal education level, although precision was limited due to the small number of cases (see eTable 2 for full results, available as Supplementary data at *IJE* online).

Discussion

In this large national cohort study, we found that the risk of CMM in childhood through young adulthood had a sinusoidal pattern by season of birth, with highest risk among persons born in spring (March–May). Because spring precedes the several-month period of highest solar UVR exposure (the main known risk factor for CMM), these findings suggest that the first few months of life may be a critical period of UVR susceptibility for the development of CMM in later life. These findings have implications for the prevention of CMM through avoidance of direct sunlight exposures among infants, especially those <6 months of age or in high-risk families, consistent with current clinical recommendations.[18] We also found other risk factors for CMM, including family history of CMM, female gender, high fetal growth and high paternal education level.

The only previous study of season of birth and CMM included 210 cases (ages 15–24 years) in northern England, and reported a sinusoidal variation among females only ($P = 0.03$), with peak risk for birth dates in March.[19] Relative risk estimates for the association between season of birth and CMM were not reported. Our larger national cohort study found that CMM risk was similarly highest among persons born in spring (March–May). However, this was found in the entire population, irrespective of gender, and across a wider age range. In addition, we found that spring birth was specifically associated with superficial spreading (but not nodular) subtype of CMM. Because superficial spreading melanoma has been more strongly associated with sun exposures,[20,21] this finding also supports a solar UVR mechanism for the seasonal variation that we observed.

The link we found between spring birth and CMM is consistent with experimental evidence for the effects of UVR exposure in infancy. UVR is capable of directly stimulating melanin production in neonatal melanocytes or melanoma cells *in vitro*.[22] A pigmentation response to solar UVR exposure has also been observed *in vivo* in the first summer of life.[4] These effects may increase the risk of CMM in individuals who lack the protective mechanism of high basal concentrations of melanin.[3,4] Our population-based findings support the hypothesis that early infancy is an important period of UVR susceptibility for the development of CMM. Later sun exposure patterns and vitamin D levels may modify these relationships and warrant further study to elucidate their relative influences.

We also found that high fetal growth was a risk factor for CMM in childhood through young adulthood. This is

consistent with some[8,23] but not all[9,10,24] previous smaller studies, most of which were case-control studies[8–10] or examined older adults.[24] The largest previous cohort study included 847 CMM cases in Denmark, and reported a modest positive trend for CMM risk by higher birthweight [relative risk (RR) per 500-g increase = 1.14; 95% CI, 1.00-1.31].[23] Differences in sun exposure patterns are a possible explanation for this finding, although high birthweight has also been associated with other cancers, especially breast cancer, via other putative mechanisms.[23,25] These mechanisms are not well established but may involve a larger number of tissue stem cells which carry a greater capacity for oncogenic mutations later in life,[26] or increased levels of growth factors such as insulin-like growth factors I and II which are correlated with birthweight and have been shown to inhibit cell apoptosis and promote tumour growth.[27,28]

The strong associations we found with family history of CMM are consistent with earlier findings[29] and may reflect shared sun exposure patterns as well as possible genetic factors. An estimated 5% of all CMM cases occur in a familial setting with two or more close relatives affected, and susceptibility genes (e.g. CDKN2A and CDK4) have been identified in such families.[7] Consistent with other European studies and in contrast to Australia, New Zealand or North America, we found a higher risk of CMM among females,[8,9,29] likely related to gender differences in sun exposure patterns which vary across different countries.[1,7] High paternal education level (an indicator of high socioeconomic status) was also a risk factor and may be related to more frequent recreational sun exposure.[7]

We found a possible trend of decreasing CMM risk by later birth order, which is in the same direction as that reported in several other studies.[8,10–12,29] Various hypotheses have been proposed, including an immunoprotective effect resulting from earlier exposure to infectious agents from older siblings,[8] or decreased opportunities for recreational sun exposure in larger families.[29] In contrast to other studies, we found no relation between older maternal age and CMM in the offspring[8,10] nor a lower risk among twins compared with singletons.[30–33]

Important strengths of this study were its population-based national cohort design and large sample size, enabling more robust and generalizable inferences. The use of season of birth as a proxy for UVR exposures in early infancy is a relatively novel approach to help elucidate a specific period of susceptibility. Linkage of birth and cancer registries provided detailed information on perinatal factors and CMM incidence that was nearly 100% complete nationwide.[34,35] A cohort design prevented selection bias that may potentially occur in case-control studies, and the use of registry-based data prevented bias that may result from self-reporting. Family history of CMM was also based on registry data with virtually complete ascertainment, thus improving the reliability of those risk estimates. CMM subtype information enabled exploratory analyses of the most common subtypes.

Study limitations included the unavailability of direct assessments of solar UVR exposures. The use of season of birth as a proxy for UVR exposures in the first few months of life is inherently imprecise and involves misclassification which is non-differential with respect to the outcome (CMM). Consequently, the reported risk estimates are expected to be conservatively biased toward the null hypothesis. The risk of CMM from actual solar UVR exposures in early infancy (i.e. with reduced misclassification) may be higher. Other seasonally varying environmental exposures such as infectious agents, however, also cannot be excluded as possible contributors to the seasonal patterns we observed. In addition, the specific comparisons in our analyses (e.g. cutpoints for season of birth groups) were data-determined, hence the findings should be interpreted with caution and will require confirmation in other large cohorts.

In summary, this large national cohort study identified several risk factors for CMM among persons born in Sweden during 1973–2008, including spring birth, high fetal growth and family history of CMM. The increased risk we observed among persons born in spring, preceding the period of highest solar UVR exposures, suggests that the first few months of life may be a critical period of UVR susceptibility for the development of CMM in later life. Avoidance of sun exposures in early infancy may play an important role in the prevention of CMM in high-risk populations.

Supplementary Data

Supplementary data are available at *IJE* online.

Funding

This work was supported by the National Cancer Institute at the National Institutes of Health [grant number R03 CA171017]; the Swedish Research Council; and ALF project grant, Lund, Sweden. The funding agencies had no role in the design or conduct of the study; in the collection, analysis or interpretation of the data; nor in the preparation, review or approval of the manuscript.

Author contributions

J.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: C.C., K.S., W.S., M.A.W., J.S. Acquisition of data: K.S., J.S. Analysis and interpretation of data: C.C., K.S., W.S., M.A.W., J.S. Drafting of the manuscript: C.C. Critical revision of the

manuscript for important intellectual content: C.C. K.S., W.S., M.A.W., J.S. Statistical analysis: C.C., J.S. Obtained funding: C.C., J.S.

Conflict of interest: None declared.

References

1. Erdmann F, Lortet-Tieulent J, Schuz J et al. International trends in the incidence of malignant melanoma 1953-2008 – are recent generations at higher or lower risk? *Int J Cancer* 2013;**132**: 385–400.
2. Oliveria SA, Saraiya M, Geller AC, Heneghan MK, Jorgensen C. Sun exposure and risk of melanoma. *Arch Dis Child* 2006;**91**:131–38.
3. 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.
4. Mack MC, Tierney NK, Ruvolo E Jr, Stamatas GN, Martin KM, Kollias N. Development of solar UVR-related pigmentation begins as early as the first summer of life. *J Invest Dermatol* 2010;**130**:2335–38.
5. Abdel-Malek ZA, Kadekaro AL, Swope VB. Stepping up melanocytes to the challenge of UV exposure. *Pigment Cell Melanoma Res* 2010;**23**:171–86.
6. Rass K, Reichrath J. UV damage and DNA repair in malignant melanoma and nonmelanoma skin cancer. *Adv Exp Med Biol* 2008;**624**:162–78.
7. MacKie RM, Hauschild A, Eggermont AM. Epidemiology of invasive cutaneous melanoma. *Ann Oncol* 2009;**20**(**Suppl 6**): vi1–7.
8. O'Rorke MA, Black C, Murray LJ, Cardwell CR, Gavin AT, Cantwell MM. Do perinatal and early life exposures influence the risk of malignant melanoma? A Northern Ireland birth cohort analysis. *Eur J Cancer* 2013;**49**:1109–16.
9. Franco-Lie I, Iversen T, Robsahm TE, Abdelnoor M. Birth weight and melanoma risk: a population-based case-control study. *Br J Cancer* 2008;**98**:179–82.
10. Johnson KJ, Carozza SE, Chow EJ et al. Birth characteristics and childhood carcinomas. *Br J Cancer* 2011;**105**:1396–401.
11. Bevier M, Weires M, Thomsen H, Sundquist J, Hemminki K. Influence of family size and birth order on risk of cancer: a population-based study. *BMC Cancer* 2011;**11**:163.
12. Hemminki K, Mutanen P. Birth order, family size, and the risk of cancer in young and middle-aged adults. *Br J Cancer* 2001;**84**:1466–71.
13. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr* 1996;**85**:843–48.
14. Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and mortality in young adulthood. *JAMA* 2011;**306**: 1233–40.
15. Hosmer DW Jr, Lemeshow S. Goodness-of-fit tests for the multiple logistic regression model. *Communications in Statistics* 1980;**A9**:1043–69.
16. Efird JT, Nielsen SS. A method to model season of birth as a surrogate environmental risk factor for disease. *Int J Environ Res Public Health* 2008;**5**:49–53.
17. StataCorp. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP, 2013.
18. Balk SJ. Ultraviolet radiation: a hazard to children and adolescents. *Pediatrics* 2011;**127**:588–97.
19. Basta NO, James PW, Craft AW, McNally RJ. Seasonal variation in the month of birth in teenagers and young adults with melanoma suggests the involvement of early-life UV exposure. *Pigment Cell Melanoma Res* 2011;**24**:250–53.
20. Micu E, Baturaite Z, Juzeniene A, Bruland OS, Moan JE. Superficial-spreading and nodular melanomas in Norway: a comparison by body site distribution and latitude gradients. *Melanoma Res* 2012;**22**:460–65.
21. Naldi L, Altieri A, Imberti GL, Gallus S, Bosetti C, La Vecchia C. Sun exposure, phenotypic characteristics, and cutaneous malignant melanoma. An analysis according to different clinicopathological variants and anatomic locations (Italy). *Cancer Causes Control* 2005;**16**:893–99.
22. Friedmann PS, Gilchrest BA. Ultraviolet radiation directly induces pigment production by cultured human melanocytes. *J Cell Physiol* 1987;**133**:88–94.
23. Ahlgren M, Wohlfahrt J, Olsen LW, Sorensen TI, Melbye M. Birth weight and risk of cancer. *Cancer* 2007;**110**:412–19.
24. McCormack VA, dos Santos Silva I, Koupil I, Leon DA, Lithell HO. Birth characteristics and adult cancer incidence: Swedish cohort of over 11,000 men and women. *Int J Cancer* 2005;**115**:611–17.
25. Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI. Growth patterns and the risk of breast cancer in women. *N Engl J Med* 2004;**351**:1619–26.
26. Capittini C, Bergamaschi P, De Silvestri A, et al. Birth-weight as a risk factor for cancer in adulthood: the stem cell perspective. *Maturitas* 2011;**69**:91–93.
27. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. *Nat Rev Cancer* 2004;**4**:505–18.
28. Savarese TM, Strohsnitter WC, Low HP, et al. Correlation of umbilical cord blood hormones and growth factors with stem cell potential: implications for the prenatal origin of breast cancer hypothesis. *Breast Cancer Res* 2007;**9**:R29.
29. Olesen AV, Parner ET, Mortensen PB, Sorensen HT, Olsen J. Prenatal risk factors for cutaneous malignant melanoma: follow-up of 2,594,783 Danes born from 1950 to 2002. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:155–61.
30. Franco-Lie I, Iversen T, Tretli S, Kringlen E, Berg K, Abdelnoor M. Malignant melanoma of the skin: risk, tumour characteristics and mortality in adult twins born in Norway between 1905 and 1945 - a cohort study. *Melanoma Res* 2005;**15**:461–66.
31. Hemminki K, Li X. Cancer risks in twins: results from the Swedish family-cancer database. *Int J Cancer* 2002;**99**:873–78.
32. Iversen T, Tretli S, Kringlen E. An epidemiological study of cancer in adult twins born in Norway 1905–1945. *Br J Cancer* 2001;**84**:1463–65.
33. Neale RE, Mineau G, Whiteman DC, Brownbill PA, Murphy MF. Childhood and adult cancer in twins: evidence from the Utah genealogy. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:1236–40.
34. Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. *Scand J Soc Med* 1990;**18**:143–48.
35. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol* 1984;**23**:305–13.