Sun-Protection Behavior, Pubertal Development and Menarche: Factors Influencing the Melanocytic Nevi Development—The Results of an Observational Study of 1,512 Children

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Observational studies consistently show that melanocytic nevus prevalence increases with age and that phenotypic traits are significantly associated with nevus count in children. An observational study of 1,512 children and adolescents from 2010 to 2013 was conducted. Study dermatologists counted the full body, arm, and facial nevi of each participant. Children and their parents were asked to complete a survey to gather data on personal characteristics, pubertal development, and early-life sun exposure. The main aim of the study was to establish pediatric nevus prevalence and its relationship with age, phenotype, sex, menarche, early-life sun exposure, and sun-protection behaviors. Females had a significantly lower nevus count compared with males, but this sex-related difference was significantly modified by menarche. Sun exposure and sun-protection habits were all significantly associated with nevus count; in particular, children who used sunscreen with a sun-protection factor > 30 had a lower nevus count compared with sun-protection factor ≤ 30 sunscreen users. This study shows that sex, menarche status, and sun-protection practices significantly influence nevus count in this pediatric population.

Journal of Investigative Dermatology (2018) **138,** 2144–2151; doi:10.1016/j.jid.2018.02.046

INTRODUCTION

Melanocytic nevus count represents the most significant phenotypic risk factor of melanoma, as high nevus phenotype marks a readily identifiable melanoma-prone group that must be periodically followed to detect early malignant melanoma (Whiteman et al., 2005). Currently, this "old" concept has been overcome by the recent notion that high nevus counts are associated with lower Breslow thickness at melanoma diagnosis and confer a favorable prognosis among melanoma patients (Ribero et al., 2015). Observational studies consistently show that melanocytic nevus prevalence increases with age and that phenotypic traits are significantly associated with nevus count in children (Barón et al., 2014; Bauer et al., 2005; Buendía-Eisman et al., 2012; Gandini et al., 2005; Kallas et al., 2006; Lopez-Ravello et al., 2015; Rivers et al., 1995; Siskind et al., 2002; Whiteman et al., 2005). Although males have a worse outcome when compared with females among melanoma patients (Joosse et al., 2011, 2012, 2013; Khosrotehrani et al., 2015) and there is growing evidence to support a direct correlation between estrogens and melanoma growth and progression (De Giorgi et al., 2013; Janik et al, 2014; Mitkov et al., 2015; Spyropoulos et al., 2015), little is known about the influence of sex on nevus burden, and there is no definitive evidence that females have fewer nevi compared with males (Carli et al, 2002; Crane et al., 2009; Dulon et al., 2002; Lopez-Ravello et al., 2015; Oliveria et al., 2009). In two case-control studies, mean nevus count in an Australian cohort was not affected by sex in either adult cases or controls, whereas in a UK cohort, males had a higher nevus count compared with females (Ribero et al., 2017).

Although sunburn early in life increases the lifetime risk of developing melanoma, there is less conclusive evidence regarding the protective role of sun-protection practices and sunscreen use (Autier et al., 2007; Crane et al., 2009; Gorham et al., 2007; Green et al., 2011; Huncharek and Kupelnick, 2002; Køster et al., 2010; Olsen et al., 2015a, 2015b; Radespiel-Tröger et al., 2009; Rodvall et al., 2010; United States Environmental Protection Agency, 2011; Wolf et al., 1998).

To identify the significant predictors of nevus development in children and improve primary melanoma prevention, we

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Abbreviation: SPF, sun-protection factor

Received 15 September 2017; revised 5 February 2018; accepted 10 February 2018; accepted manuscript published online 1 April 2018; corrected proof published online 5 June 2018

built an Italian population-based cross-sectional study of nevus counts among children and adolescents. The aim of this study was to establish pediatric nevus prevalence and its relationship with age, phenotype, sex, menarche, early-life sun exposure, and sun-protection behaviors.

RESULTS

Participant characteristics

Overall, 1,512 children and adolescents aged 0 through 18 years were examined. The participation rate was 100%. The characteristics of the study subjects are detailed in Table 1. The median age of our pediatric sample was 12 years (interquartile range, 8–13 years), with a slight male predominance (n = 779, 51% males vs. n = 733, 49% females). The median number of body nevi was 10 (interquartile range, 4–20), whereas the median count of arm and face nevi was lower (2, interquartile range 0–5; 1, interquartile range, 0–3, respectively). Twenty-two percent of children had congenital melanocytic nevi and one child had a giant congenital nevus. Less than 1% of children (n = 8, 0.05%) had a previous neoplasm (i.e., acute lymphoblastic leukemia, 100%); 6% (n = 91) had a family history of melanoma (Table 1).

Phenotypic characteristics and sun exposure behavior

In the univariate analysis investigating the features associated with the proportions of children with 10 nevi or more, the phenotype-, sex-, and sun exposure-related variables considered in the study were all significantly associated with nevus count, with the exception of age at first sunburn. Fitzpatrick skin phototype was significantly associated with nevus count ($P < 0.0001$, Table 2); skin phototypes I–III had a higher nevus burden compared with phototypes IV–VI (Figure 1). Other phenotypic characteristics, as well as eye, skin, and hair color, were all associated with nevus prevalence ($P = 0.0196$, $P < 0.0001$, and $P = 0.0211$, respectively; Table 2). Fair and medium skin tones were associated with a higher count of nevi compared with olive and dark skin tones (Figure 1). Blond and brown hair was associated with a higher full body number of nevi compared with black and red hair (Figure 1). Sex and menarche were significantly associated with nevus count ($P < 0.0001$, Table 2). Indicators of sun exposure (i.e., sun exposure, outdoor/indoor sport, reason for sun exposure, sunburn history, annual duration of sun exposure, child's age at first exposure and at first sunburn) were all significantly associated with an increase in nevus count (Table 2, Figure 2); sun-exposed children had more nevi compared with nonexposed children ($P < 0.0001$). Sunscreen users had significantly more nevi than nonusers ($P = 0.004$) (Table 2). The frequency of sunscreen use was positively associated with nevus count (Figure 2); children who applied sunscreen more than two times per day had significantly more nevi compared with children who used sunscreen twice or less per day ($P = 0.006$). The sun-protection factor (SPF) of the sunscreen applied was significantly associated with nevus development, as children who used sunscreen with an SPF > 30 had a significant decrease in nevus count compared with SPF ≤ 30 sunscreen users ($P = 0.008$, Table 2).

Multivariate analysis

Multivariate regression models were performed to analyze the association of full body nevus count and nevus count on the face and arms with age, sex, phototype and other phenotypic traits, sunburn frequency, and sunscreen use. The adjusted multivariate analysis confirmed that many phenotypic characteristics and sun exposure habits influenced nevus count.

Nevus count was significantly associated with age and sex, even after accounting for the effects of phenotypic traits and sun exposure habits (Table 3). Children older than 12 years (median age of the population) had more nevi on the whole body, face, and arms than children 12 years or younger ($E = 0.305$, $P = 0.0005$; $E = 0.154$, $P < 0.0001$; and $E = 0.208$, $P = 0.0002$, respectively). Females had a significantly lower nevus count compared with males, but this sex-related difference was significantly modified by menarche, despite adjustment for age. The female advantage in terms of nevus burden over males was significant only in post-menarche females ($E = -0.156$, $P = 0.0078$ and $E = -0.257$, $P = 0.001$ for facial and total body nevi,

Table 1. Characteristics of the study subjects

Characteristics	Median (IQR)	n (%)
Age	12 (8–13)	1,512
Sex		
Female		733 (49)
Male		779 (51)
BMI	19 (17–21)	
Full-term birth		
Missing		45 (3)
No		187 (12)
Yes		1,280 (85%)
Breastfeeding		
Missing		13 (1)
No		194 (13)
Yes		1,305 (86)
Menarche age	12 (11–12)	
Total nevi	10 (4–20)	
0		147 (9.8)
1–10		754 (49.9)
11–20		347 (23)
21–50		245 (16)
51–99		15 (1)
≥100		4 (0.3)
Arm nevi, n	2 (0–5)	
Facial nevi, n	1 (0–3)	
Congenital nevi		
No		1,176 (78)
Small		229 (15)
Medium		106 (7)
Giant		1 (1)
Angiomas or other skin malformations		
No		1,217 (80.49)
Angiomas		167 (11.04)
Other		128 (7.57)
Previous neoplasms		
No		1,504 (99.5)
Yes		8 (0.5)
Family history of melanoma		
Missing		14 (1)
No		1,407 (93)
Yes		91 (6)

Abbreviation: BMI, body mass index.

Table 2. Proportions of subjects by phenotypical factors, indicator of UV exposure, and number of nevi

	Total nevi < 10 n (%)	Total nevi ≥ 10 n (%)	*P*-value
	901	611	
Sex and menarche			
Males	432 (47.95)	347 (56.79)	<0.0001
Pre-menarche	308 (34.18)	119 (19.48)	
Post-menarche	161 (17.87)	145 (23.73)	
Fitzpatrick phototype			
I	13 (48.15)	14 (51.85)	<0.0001
II	504 (56.95)	381 (43.05)	
III	310 (60.19)	205 (39.81)	
IV	60 (84.51)	11 (15.49)	
V–VI	14 (100)	0 (0)	
Eye color			
Dark	643 (60.89)	413 (39.11)	0.0196
Green	135 (62.21)	82 (37.79)	
Blue	121 (51.05)	116 (48.95)	
Grey/hazel	2 (100)	0 (0)	
Skin color			
Fair	328 (57.85)	239 (42.15)	<0.0001
Medium	329 (53.93)	281 (46.07)	
Olive	212 (70.2)	90 (29.8)	
Dark	32 (96.97)	1 (3.03)	
Hair color			
Red	10 (76.92)	3 (23.08)	0.0211
Blond	167 (60.07)	111 (39.93)	
Brown	630 (57.9)	458 (42.1)	
Black	94 (70.68)	39 (29.32)	
Sun exposure			
No	31 (100)	0 (0)	<0.0001
Yes	870 (58.74)	611 (41.26)	
Sunscreen			
No	114 (69.94)	49 (30.06)	0.004
Yes	787 (58.34)	562 (41.66)	
Frequency of sunscreen use per day median (IQR)			
2 (1–3)	2 (1–3)	2 (1–3)	0.004
0–2	659 (61.82)	407 (38.18)	0.006
>2	240 (54.18)	203 (45.82)	
SPF median (IQR)[1]			
40 (25–50)	50 (30–50)	30 (20–50)	<0.0001
≤30	295 (50.34)	291 (49.66)	<0.0001
>30	399 (67.86)	189 (32.14)	
Sport			
No	325 (76.83)	98 (23.17)	<0.0001
Outdoor	183 (47.66)	201 (52.34)	
Indoor	343 (58.73)	241 (41.27)	
Both	50 (41.32)	71 (58.68)	
Reason for sun exposure			
Holidays	770 (61.85)	475 (38.15)	<0.0001
Sport/leisure	29 (76.32)	9 (23.68)	
Holidays + leisure and leis leisure	102 (44.54)	127 (55.46)	
Sunburns no. of sunburns per day: median (IQR)			
0 (0–2)	0 (0–1)	1 (0–3)	<0.0001
No	553 (67.6)	265 (32.4)	<0.0001
Yes	348 (50.14)	346 (49.86)	

(*continued*)

Table 2. Continued

	Total nevi < 10 n (%)	Total nevi ≥ 10 n (%)	*P*-value
Age at first sunburn (y) median (IQR)			
7 (5–9)	7 (5-–10)	7 (5–9)	0.585
>7 y	145 (49.66)	147 (50.34)	0.827
≤7 y	203 (50.5)	199 (49.5)	
Duration of sun exposure (d) median (IQR)[1]			
21 (14–40)	20 (14–30)	21 (15–45)	0.001
>21 d	504 (62.07)	308 (37.93)	0.038
≤21 d	396 (56.81)	301 (43.19)	
Age at first exposure (mo) median (IQR)[1]			
21 (14–40)	12 (7–24)	24 (12–36)	<0.0001

P-value from the chi-square test or the Wilcoxon rank test.
Abbreviation: IQR, interquartile range; SPF, sun-protection factor.
[1]Among users/exposed.

respectively); we found no significant difference in nevus count between males and pre-menarche females ($P = 0.411$ and 0.217 for facial and total body nevi, respectively). The advantage over males in lower nevus count on arms was significant in pre- and post-menarche girls ($E = -0.147$, $P = 0.025$ and $E = -0.210$, $P = 0.004$, respectively). The presence of congenital nevi was positively associated with nevus count: children with congenital nevi have a greater number of common nevi ($E = 0.178$, $P < 0.0001$; $E = 0.293$, $P < 0.0001$; and $E = 0.135$, $P = 0.012$ for facial, total body, and arm nevi, respectively) (Table 3). Skin color was significantly associated with nevus count; in particular, children with fair and medium skin tones had a higher nevus count on the whole body compared with dark-skinned subjects ($E = 0.545$, $P = 0.0013$ and $E = 0.541$, $P = 0.0014$ for fair and medium skin color, respectively).

Sun exposure behavior significantly influenced nevus prevalence. Age at first sun exposure was significantly associated with nevus count ($E = 0.005$, $P = 0.001$; $E = 0.008$, $P = 0.001$; $E = 0.004$, $P = 0.001$ for facial, total body, and arm nevi, respectively). The number of nevi significantly increases with the number of days per year spent on intentional intermittent sun exposure (i.e., sun exposure associated with willingness to get a tan or to stay longer in the sun, Autier et al., 2007) ($E = 0.002$, $P = 0.012$ and $E = 0.004$, $P = 0.001$ for full body and arm nevi, respectively).

After adjusting for confounders, phenotypical characteristics, and sun exposure habits, the sunscreen SPF level remained significantly associated with nevus count: nonsunscreen users had significantly more nevi compared with children who used high-SPF sunscreens (SPF > 30) ($E = 0.645$, $P = 0.0053$ and $E = 0.436$, $P = 0.0432$ for total body and arm nevi, respectively); children who used sunscreen with a low-medium SPF protection (SPF ≤ 30) had significantly more nevi than high-SPF sunscreens (SPF > 30) users ($E = 0.154$, $P = 0.0002$; $E = 0.288$, $P < 0.0001$; and $E = 0.135$, $P = 0.0083$ for facial, total body, and arm nevi, respectively, Table 3). On the other hand, the daily frequency of sunscreen use was positively associated with nevus count; children who applied sunscreen more than twice

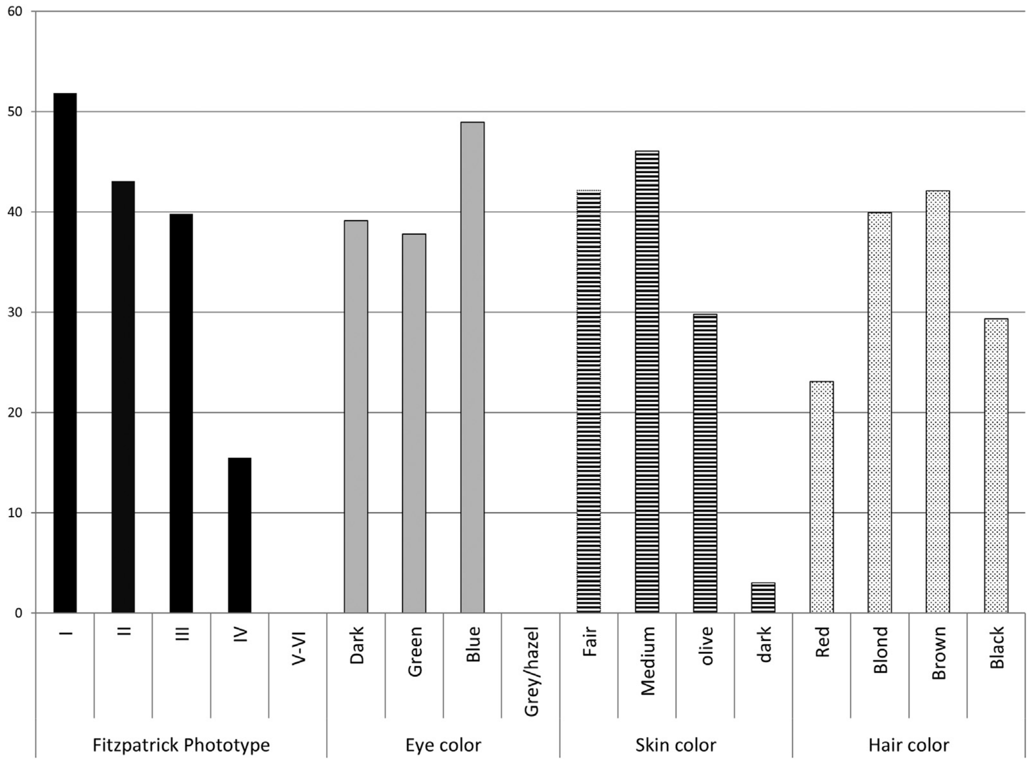

Figure 1. Histogram of percentages of children with more than 10 nevi by phenotypic characteristics.

a day had a higher number of arm nevi compared with those who did not repeat the application of sunscreen during sun exposure ($E = -0.708$, $P = 0.0034$ and $E = -0.555$, $P = 0.0135$ for total and arm nevi, respectively). A history of sunburn was also associated with an increase in nevus count ($E = 0.153$, $P = 0.0001$; $E = 0.239$, $P < 0.0001$; and $E = 0.112$, $P = 0.0223$ for facial, total, and arm nevi, respectively, Table 3). Participation in sport was positively associated with nevus count; children who did not play sports had fewer nevi than children who participated in outdoor and/or indoor sport ($E = -0.389$, -0.790, and -0.415, $P < 0.0001$ for facial, total body, and arm nevi, respectively).

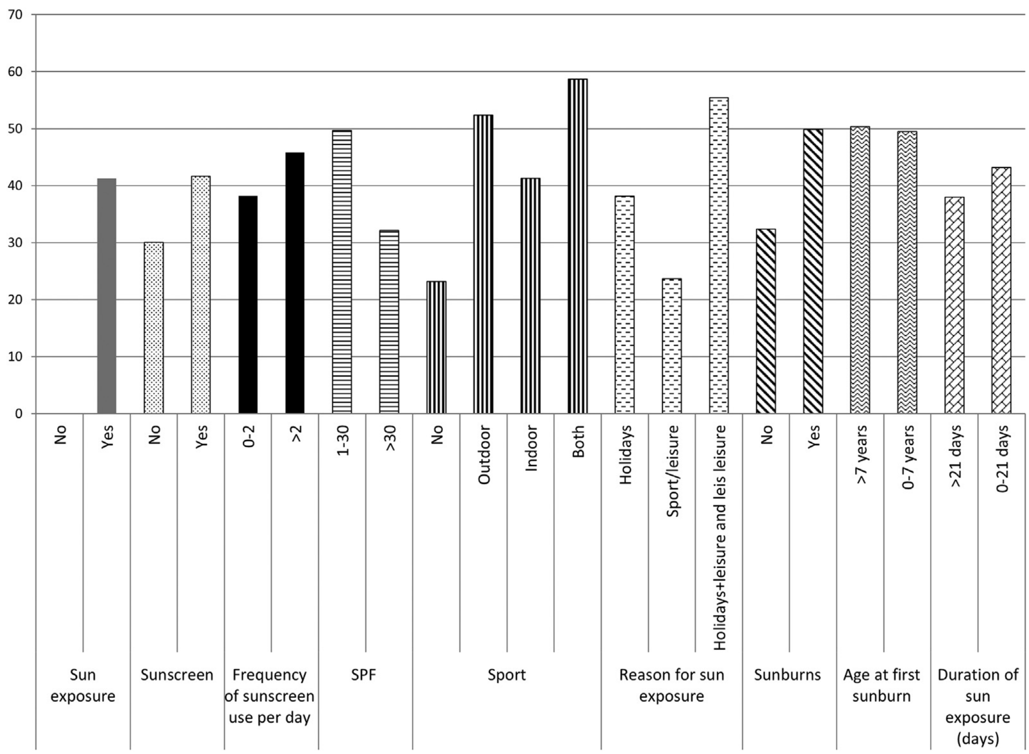

Figure 2. Histogram of percentages of children with more than 10 nevi by indicators of sun exposure.

Table 3. Multivariate analyses: factors associated with number of nevi

	Parameter	Comparisons	Estimate	SE	*P*-value
Facial nevi	Intercept		0.550	0.149	0.0002
	Sex	Females pre-menarche vs. males	0.043	0.052	0.4106
		Females post-menarche vs. males	−0.156	0.059	0.0078
	Age	>12 vs. ≤12	0.154	0.044	0.0005
	Congenital nevi	Yes vs. no	0.178	0.043	<0.0001
	Skin color	Fair vs. dark	0.235	0.127	0.0649
		Medium vs. dark	0.299	0.127	0.0188
		Olive vs. dark	0.134	0.128	0.297
	Age at the start of sun exposure (mo)		0.005	0.004	0.001
	Sport	No vs. indoor and outdoor	−0.389	0.074	<0.0001
		Outdoor vs. indoor and outdoor	−0.062	0.075	0.4096
		Indoor vs. indoor and outdoor	−0.170	0.070	0.0161
	SPF	No vs. >30	−0.073	0.058	0.2144
		≤30 vs. >30	0.154	0.041	0.0002
	Sunburns	Yes vs. no	0.153	0.039	0.0001
Total nevi	Intercept		1.546	0.203	<0.0001
	Sex	Females pre-menarche vs. males	−0.086	0.070	0.2168
		Females post-menarche vs. males	−0.257	0.078	0.001
	Age	>12 vs. ≤12	0.305	0.059	<0.0001
	Congenital nevi	Yes vs. no	0.293	0.058	<0.0001
	Skin color	Fair vs. dark	0.545	0.169	0.0013
		Medium vs. dark	0.541	0.169	0.0014
		Olive vs. dark	0.219	0.171	0.1988
	Age at the start of sun exposure (mo)		0.008	0.004	0.001
	Days of exposure per year		0.002	0.001	0.0124
	Sport	No vs. indoor and outdoor	−0.790	0.100	<0.0001
		Outdoor vs. indoor and outdoor	−0.040	0.101	0.6884
		Indoor vs. indoor and outdoor	−0.146	0.095	0.1229
	Frequency of sunscreen use per day	No vs. >2 times	−0.708	0.241	0.0034
		1−2 vs. >2 times	−0.011	0.055	0.8489
	SPF	No vs. >30	0.645	0.231	0.0053
		≤30 vs. >30	0.288	0.055	<0.0001
	Sunburns	Yes vs. no	0.239	0.052	<0.0001
Nevi on arms	Intercept		0.753	0.189	<0.0001
	Sex	Females pre-menarche vs. males	−0.147	0.065	0.0246
		Females post-menarche vs. males	−0.210	0.073	0.0039
	Age	>12 vs. ≤12	0.208	0.055	0.0002
	Congenital nevi	Yes vs. no	0.135	0.054	0.0121
	Skin color	Fair vs. dark	0.361	0.157	0.0217
		Medium vs. dark	0.348	0.157	0.0268
		Olive vs. dark	0.060	0.159	0.7071
	Age at the start of sun exposure (mo)		0.004	0.003	0.001
	Day of exposure per year		0.003	0.001	0.001
	Sport	No vs. indoor and outdoor	−0.415	0.093	<0.0001
		Outdoor vs. indoor and outdoor	0.031	0.094	0.741
		Indoor vs. indoor and outdoor	−0.034	0.088	0.7015
	Frequency of sunscreen use per day	No vs. >2 times	−0.555	0.225	0.0135
		1−2 vs. >2 times	−0.095	0.052	0.066
	SPF	No vs. >30	0.436	0.215	0.0432
		≤30 vs. >30	0.135	0.051	0.0083
	Sunburns	Yes vs. no	0.112	0.049	0.0223

P-values are obtained from the multivariate linear regression model; number of nevi is the dependent variable. Number of nevi (+1) was log-transformed to reach normality of residuals of the full model.

Abbreviations: SE, standard error; SPF, sun-protection factor.

DISCUSSION

The median number of nevi per child was lower in our pediatric population in comparison to other studies of young populations from the Mediterranean (Buendía-Eisman et al., 2012; Huncharek and Kupelnick, 2002; Lopez-Ravello et al., 2015). In agreement with previously published results (Lopez-Ravello et al., 2015; Muñoz Negro et al., 2011; Paláu-Lázaro et al., 2008), we found an increased number of melanocytic nevi in children over the age of 12 years. Children with high nevus counts were significantly more likely to have fair phenotypic traits, especially those with a fair/medium skin tone (Whiteman et al., 2005).

Although there are conflicting results for the relationship between nevus count and sex (Carli et al, 2002; Crane et al., 2009; Dulon et al., 2002; Lopez-Ravello et al., 2015; Oliveria et al., 2009; Vogelstein and Kinzler, 2016), we found that males have more nevi than females. This sex-related difference in nevus count was significant only after menarche, which suggests that menarche may represent a key event in nevus development. We do not have enough reliable data to analyze the potential effect of puberty on nevus development among males, as there is no clear-cut landmark for male puberty, and male adolescents may be more reluctant than females to discuss this topic with adults. At present, we can only hypothesize that hormonal changes due to menarche may contain melanocytic proliferation and justify the female advantage in terms of nevus burden.

Our data confirmed that, after adjustment for confounders and phenotypical traits, sunburn is a strong predictor of nevus count among children, as well as age at first sun exposure and participation in outdoor sports. Sunscreen users, when compared with nonusers, were more likely to develop nevi. Moreover, unlike other pediatric analyses (Whiteman et al., 2005), a higher frequency of daily application of sunscreen was associated with a higher nevus count. As suggested by other studies (Green et al., 2011; Olsen et al., 2015a, 2015b), the use of high-SPF (>30) sunscreens exclusively, when compared with the use of sunscreens with SPF $\leq$ 30, adequately protected skin during sun exposure and significantly reduced nevus burden.

Until now, studies have been inconclusive regarding sunscreen use and the development of nevi among children, with a single randomized trial showing evidence of benefit (Gallagher et., 2000; Oliveria et al., 2009), whereas other studies have shown a positive association between sunscreen use and nevus prevalence (Azizi et al., 2000; Darlington et al., 2002; Dulon et al., 2002; Luther et al., 1996). The possible explanation of our emerging findings may be interpreted in the light of two considerations. First, children who apply more sunscreen are usually fair-skinned subjects with freckles and tend to be burnt by the sun easily, and, consequently, lower skin phototypes have a greater tendency to develop sunburn and nevi. As shown in Table 2, there was a predominance of high-risk children with low phototype (I—III) in our study population. Second, the anti-erythematous effect and a false sense of protection against sunburn conferred by frequent sunscreen application may lead children to spend more time in the sun and to expose themselves in the middle of the day when UV rays are stronger (Rodvall et al., 2010). However, although these explanations are plausible, our findings regarding sunscreen use remained significant in the multivariate analysis after adjustment for skin color and sunburn history. Finally, the choice of sunscreen may be inappropriate. Children should use water-resistant and broad-spectrum (i.e., sunscreen that protects against UVA and UVB rays) sunscreens (Planta, 2011), but during our survey, no further information about the quality of UV coverage was required in addition to the SPF. Unlike chronic, low-grade sun exposure (Godar et al., 2009; Kaskel et al., 2001; Planta, 2011; Radespiel-Tr̋oger et al., 2009; Wolf et al., 1998), our results confirm that acute intermittent exposure in childhood increases the development of nevi, which represents the most important melanoma phenotypic risk factor.

The main limitation of this cross-sectional study is represented by potential biases with self-reported data regarding sun exposure habits and sun-protection practices. Indeed, the validity of these self-reported may be unreliable, as participants' parents may have answered to portray themselves in a good light. The most likely source of error is the confusion arising from the several interrelated factors associated with sun exposure and sun-protection habits.

This observational study presents exploratory analyses on several hypotheses of possible associations and sources of bias; therefore, the issue of multiple testing should be always taken into account and results are not conclusive.

In summary, although caution is needed in drawing firm conclusions because this analysis is an observational study and not a clinical trial, the clinical importance of our findings suggests that further detailed, more structured studies should be addressed to define the relationship between the development of nevi in children and phenotypic, hormonal, and environmental factors. Particularly, the relationship between puberty and increased nevus burden should be investigated in both sexes. Moreover, information gathering about sun exposure and sunscreen use should be more systematic, including more detailed questions regarding sunscreen application in the study survey (e.g., when used, how much used, or how often it was reapplied). Finally, we did not consider how many hours the children spend out in the sun on a typical summer weekend day at the beach and the amount of time spent outside in the sun between the hours of 11 am and 4 pm. Nonetheless, the high number of pediatric participants and the broad spectrum of features considered (i.e., phenotypic and environmental) make our findings help identify the principal characteristics associated with a higher nevus count in children.

The question of whether our current advice regarding sunscreen use in children is truly beneficial or detrimental in the fight against melanoma is still a priority, and sunscreen should not be used by parents to extend the amount of time children spend in the sun. The systematic use of high-SPF sunscreen (SPF > 30) in children should be part of an overall sun-protection strategy that includes avoidance of exposure to midday sun and the use of protective clothing and hats (Planta, 2011). The above considerations justify the implementation of primary prevention campaigns focused on sun-protection education for children, especially in schools.

MATERIAL AND METHODS

Participant recruitment and survey

A cross-sectional descriptive study was conducted involving Italian children and adolescents aged 0 through 18 years, who were referred to the Pediatric Dermatology clinic, Anna Meyer Pediatric Hospital, or the Dermatology Clinic, Department of Dermatology, Florence, Italy, for first-level dermatologic visits for various reasons (e.g., atopic dermatitis, psoriasis, nevi, eczema, lichen planus, etc.) from 1 January 2010 to 31 December 2013. All children who visited these clinics were enrolled. The study was approved by the local institutional review board. During the clinic visit, parents were asked for written, informed parental consent to perform a total body skin examination to assess their child's nevus count. At least one parent was present with the child during the clinic visit. Two study dermatologists with 5 years' experience in the diagnosis of pigmented lesions counted the full body, arm, and facial nevi of each participant (Argenziano et al., 2014). Because of the potential misdiagnosis of nevi as freckles, we used a diameter of 2 mm as the lower sized cutoff for the assessment of nevi (Oliveria et al., 2009). To minimize any bias or misclassification, nevus counts were validated by a second dermatologist.

After the total body skin examination, children and their parents were asked to complete a survey to gather data on personal characteristics (e.g., weight, height, term birth, breastfeeding, menarche, indoor and/or outdoor sport and activities, previous noncutaneous tumors, family history of melanoma), phenotypic data (e.g., eye color, hair color, and skin pigmentation), skin phototype according to the Fitzpatrick scale (scale I–VI), assessed by the study dermatologists through physical examination and parent interview, and early-life sun exposure. Parents were asked to answer questions on early-life sun exposure (age at first sun exposure, reasons for exposure to the sun—i.e., recreation, vacation, outdoor activities—duration of sun exposure in terms of number of days per year, history of sunburn, age at first sunburn), sun-protection practices over the past 5 years (sunscreen use, frequency of sunscreen use, SPF, and use of tanning beds). The second part of the survey questionnaire was compiled by the physician and included the number of total body, arm, and face nevi; the presence of congenital melanocytic nevi (i.e., those present at birth; small <1.5 cm, medium 1.5–19.9 cm, giant ≥ 20 cm in diameter, respectively); atypical nevi; and other skin findings.

Statistical analysis

The goal of this analysis was to identify the individual and behavioral characteristics associated with nevus phenotype, which is defined as the total number of nevi and the number of nevi on the face and arms. The number of nevi was log-transformed after adding a constant of 1 to account for the study subjects without any nevi, and it was used as the outcome (dependent variable) in the analyses. The choice of log transformation was influenced by its established variance-stabilizing properties, and we achieved normality of residuals of the full model. Multivariate linear models were used to identify the variables (individual and behavioral characteristics) significantly associated with nevus counts. Residuals were checked to assess normal distributions. We also used logistic models to assess variables associated with the presence of atypical nevi.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

We thank the children and the parents whose participation made this study possible. We also thank the Rotary Club Firenze Valdisieve, Italy, district 2071, for logistical and emotional support.

AUTHOR CONTRIBUTIONS

VDG 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. VDG, SG, and AG contributed to the study concept and design. AG, IS, BA, MG, SR, FP, FS, AJ, AD, and LS acquired the data. VDG and SG analyzed and interpreted the data. AG, VDG, and SG drafted the manuscript. VDG, AG, and SG involved in the critical revision of the manuscript for important intellectual content. VDG supervised the study.

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