Melanocytic Nevus Development in Colorado Children Born in 1998

A Longitudinal Study

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Objective: To describe the development of nevi from 3 to 8 years of age in a birth cohort of children in Colorado.

Design: Longitudinal observational study.

Setting: Large managed care organization and university and private primary care practices.

Participants: Annual convenience samples of children born in 1998 (range, n=137 to n=870) (participation rates, 18.8%-76.0%). We recruited children through the managed care organization, private primary care practices, and community settings.

Main Outcome Measures: Total whole body nevus counts, counts by nevus diameter (<2, 2 to <5, or ≥5 mm), and counts for chronically and intermittently exposed body sites.

Results: Non-Hispanic white children had significantly more nevi than did other racial/ethnic groups and developed an average of 4 to 6 new nevi per year from 3 to 8 years of age. Non-Hispanic white boys had significantly more nevi than did girls beginning at 6 years of age (median, 21 [interquartile range, 28] vs 17 [17]; $P=.002$). This difference was due to nevi of less than 2 mm and nevi in chronically exposed body sites. Development of new nevi leveled off in chronically exposed body sites at 7 years of age and at a higher level for boys than girls.

Conclusions: Children in Colorado developed more small nevi and fewer large nevi compared with children in other regions of the world, highlighting the importance of studying nevus development in various locations where sun exposure patterns and behavioral norms vary. The sex difference in nevus development could be owing to variation in sun exposure and/or a biological predisposition of boys to develop more nevi. Studies of nevus development can aid in the understanding of the complicated relationship between nevus development and malignant melanoma.

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THE INCIDENCE RATE FOR MAlignant melanoma nearly tripled for white individuals in the United States from 1975 to 2004,[1] making melanoma the cancer with the fastest rising incidence rate in the United States. Melanoma rates in the United States are on a trajectory that mirrors Australia, where melanoma rates are the highest in the world.[2] The presence of numerous melanocytic nevi is the strongest risk factor for melanoma.[3] Most nevi are developed in childhood, and several factors have been consistently shown to be related to higher numbers of nevi in childhood, including lighter skin, lighter hair color, blue or green eyes, and higher levels of sun exposure.[4-8] Because the risk factors for nevi closely match the risk factors for melanoma and because the number of nevi is the strongest risk factor for melanoma, nevi are studied as intermediate markers for melanoma, and understanding nevus development could lead to a better understanding of the causes of melanoma.

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White populations are at considerably higher risk for malignant melanoma than are other racial/ethnic groups. In the United States, non-Hispanic white individuals had an annual incidence rate of 25.1 per 100 000 population for the period 2000 through 2004 compared with 1.0 per 100 000 for black, 4.5 per 100 000 for Hispanic white, 1.5 per 100 000 for Asian, and 2.9 per 100 000 for American Indian/Alaskan Native individuals.[1] Thus, most previous studies of nevus development have focused exclusively on white populations. Previous nevus studies in children have generally been cross-sectional, examining risk factors for nevi at a single time, whereas a few studies have followed up cohorts of children from a baseline measure of nevi to a follow-up measure 3 to 5 years later.[4,9,10] To our knowledge, no previous published studies have followed up children from a single population annually for a period of years before their 10th birthdays so that annual accumulations of nevi could be studied. Studies that examine nevus development on at least an annual basis are important because they have the potential to identify developmental periods of greatest increase in nevi. Longitudinal studies in different geographic conditions (eg, latitude, altitude, and climate) and in populations with different behavioral patterns (eg, clothing styles and outdoor activity patterns) are imperative to understanding melanoma risk, including understanding whether a threshold of sun exposure during childhood exists at which additional exposure conveys no further risk, as has been suggested by researchers in Australia.[11] Such a threshold could be reached at different ages under different geographic and social conditions.

The present study is, to our knowledge, the first annual longitudinal study of nevus development in children in the United States. Children born in 1998 and residing in the metropolitan area constituted by Denver and Boulder, Colorado, were examined each year from 2001 through 2006 (at 3-8 years of age). We traced nevus development over time by race/ethnicity and among non-Hispanic white children, by sex for all nevi, by nevi smaller than 2 mm and 2 mm or more in diameter, and by nevi on chronically and intermittently exposed skin.

METHODS

STUDY POPULATION

This nevus study was conducted as part of 2 behavioral intervention trials aimed at increasing sun protection practices of parents for their young children. Children born from January 1 to September 30, 1998, were eligible. Initial recruitment in 1998 was conducted through a large managed care organization (MCO) that serves 29% of the insured population of the Denver/Boulder metropolitan area. Hospital birth logs were used to identify all births, and mothers were contacted by telephone for enrollment before the child was 6 months of age. The recruitment interview included a screening of skin cancer risk, and parents whose children had dark skin color, dark eye color, and dark hair color were informed that the program may be of minimal benefit to their child because of low skin cancer risk. Otherwise, all families were invited to participate. From a total of 2148 births, we contacted 1177 eligible families and recruited 728 (61.9%). Skin examinations were conducted in 2001 and 2002 (at 3 and 4 years of age) on this sample. Subjects were randomly assigned to a control group or behavioral intervention group according to the managed care clinic at which they were enrolled (7 clinics in each group). The control group received standard care and the intervention group received anticipatory guidance for sun protection at well-child visits from 2 to 36 months of age.[12] The behavioral intervention did not affect nevus development by 3 years of age.[12]

Additional children were recruited for a second behavioral intervention trial in the fall of 2003 and winter of 2004. Owing to new restrictions governing patient privacy (the Health Insurance Portability and Accountability Act), we were unable to contact parents directly from health care system enrollment records, so mailings were sent to eligible families attending the MCO described in the previous paragraph and 7 large private pediatric practices. Parents were asked to return a card if they were interested in participating and then were telephoned by study interviewers who explained the study and followed the same enrollment protocol as described for the 1998 enrollment. In addition, we recruited some families through community retail sites, recreational facilities, and schools. Participating children were not required to have been born in Colorado; 166 of 867 (19.1%) were born outside the state. Because the study team was not given access to patient names, the participation rate for the study among those invited is not known.

The second behavioral trial was conducted from 2004 to 2007 and included sun protection educational mailings to parents and children based on the Precaution Adoption Process Model.[13] Children also received sun protection resources such as sun hats, swim shirts, sunscreen, tree seeds, a backpack, and sun-protection learning activities. Individual children among those newly recruited were assigned at random to the intervention group or to a standard care control group. All children continuing from the sample recruited in 1998 (n=278) were assigned to the intervention group.

All study procedures were reviewed and approved by the Colorado Multiple Institutional Review Board and the institutional review board of Kaiser Permanente of Colorado. Parents provided written informed consent before the skin examinations. Beginning at 7 years of age, children provided written assent for participation.

SKIN EXAMINATIONS

Skin examinations provided information on the distribution and size of nevi; phenotypic factors including height, weight, and pigmentation of the skin, hair, and eyes; and the degree of tanning and freckling. Observation of hair color used hair samples and was coded into the following 5 categories: red, blonde, light brown, medium brown, and dark brown or black. Eye color was recorded as blue, green, brown, or hazel (any combination of brown with another color). Height and weight were measured using standard clinical procedures. Freckling on the face was assessed using a 10-level chart.[14] Skin color and degree of tanning were measured using a colorimeter (Minolta Chroma Meter CF-300 or CR-400; Konica Minolta Sensing, Inc, Osaka, Japan), which quantifies color using the 3-dimensional L a b system. Using the b dimension,[15] base skin color was measured on the unexposed, upper medial arm, and the degree of tanning was calculated as the difference in b-dimension values in this area and the exposed lateral forearm. Skin color and tanning values were the mean of 5 measurements.

Nevus examinations were conducted each summer by a team of 4 to 7 health care providers who received annual training from the study's lead dermatologist (J.G.M.). The entire body was examined for nevi, with the exception of the scalp, genitals, and buttocks. Nevi were defined as any size of pigmented macules or papules, excluding freckles, café au lait macules, and warts. Nevi were differentiated from freckles and café au lait macules by the fact that only nevi are raised and that flat, early junctional nevi are dark brown, have regular edges, and do not occur in patches as freckles do. Lentigines were expected to be rare in this young population. The size of the nevus was determined using a clear plastic stencil with cutouts for 2 and 5 mm. Nevi were classified as less than 2, at least 2 to less than 5, or at least 5 mm in diameter. Nevi were recorded by size on a standardized body map. Congenital nevi were recorded separately and excluded from overall nevus counts. All examiners participated in duplicate examinations each year to determine interrater reliability. Interrater reliability coefficients (calculated using the intraclass correlation) for 2001, 2002, 2003, 2004, 2005, and 2006 were 0.82 (n=48), 0.89 (n=22), 0.97 (n=7), 0.89 (n=33), 0.80 (n=48), and 0.85 (n=66), respectively.

With the exception of 2003, skin examinations were conducted from mid-June to early October each year so that tanning during the warmer months could be observed. In 2003, skin examinations were delayed because of funding and study enrollment issues and were conducted from late October 2003 to March 2004. Thus, an interval of approximately 12 months can be assumed between examinations for all years except 2003. In 2003, skin examinations were conducted on average 17 months after the 2002 examinations and only 7 months before the 2004 examinations.

PARTICIPATION RATE IN SKIN EXAMINATIONS

There were 728 children enrolled at the beginning of the study in 1998. Of these, 281 (38.6%) participated in skin examinations in 2001, and 137 (18.8%) participated in 2002. Following the next phase of recruitment in 2003 to 2004, a total of 1145 children were enrolled, of whom 278 (24.3%) were from the original sample. Participants in the skin examinations in subsequent years included 284 (24.8%) in 2003, 856 (74.8%) in 2004, 870 (76.0%) in 2005, and 860 (75.1%) in 2006. The primary factor that distinguished data collection in 2001 and 2002 from data collection in subsequent years was the offering of an incentive ($25) for attendance in 2003 to 2006. Many of the 1145 children were recruited in the spring of 2004 after the 2003 examinations had been completed, which resulted in a lower participation rate in 2003.

MEASUREMENT OF OTHER VARIABLES

Race/ethnicity was reported by the parent and categorized as non-Hispanic white, Hispanic white, black, Asian/Pacific Islander, Native American, or other.

Body sites were classified as chronically or intermittently exposed on the basis of previous research.[16] Chronically exposed sites included the face, anterior neck, lateral forearms, dorsa of the hands, and, for boys, posterior neck. Rarely exposed sites (the medial aspects of the arms, palms, and bottoms of the feet) were combined with intermittently exposed sites because they are minimal in body area and, because of the small number of nevi present, could not be analyzed separately. Intermittently exposed sites were the chest and abdomen, back and shoulders, lateral upper arms, legs, dorsa of the feet, and, for girls only, posterior neck.

DATA ANALYSIS

Because not all children participated in examinations each year and because of a second recruitment phase in 2003 to 2004 resulting in the inclusion of 867 new subjects, we conducted this analysis as 5 separate cross-sectional samples. After verifying the expected large difference in the number of nevi by race/ethnicity, subsequent analyses were restricted to non-Hispanic white children (80%-90% of the sample, depending on the year). For non-Hispanic white children, sex, phenotypic data (eye color, hair color, and skin pigmentation), size (height and weight), and levels of freckling and tanning are presented separately for each annual sample.

Nevus counts showed a positively skewed distribution, with a few children having very high counts; thus, median counts are presented. Nevi measuring at least 5 mm were very infrequent and were therefore collapsed with nevi measuring at least 2 mm. Median numbers of total nevi, of both sizes of nevi (<2 and ≥2 mm), and of nevi for chronically vs intermittently exposed skin areas were calculated for each annual sample for non-Hispanic white children by sex. Medians are presented in graphs in which significant differences are noted. We used the Mann-Whitney test (for 2-group comparisons) or the Kruskal-Wallis test (for multiple-group comparisons), which test for a location shift in the overall distributions. We elected to analyze nevus counts rather than nevus density because the children were all born within a 9-month period and thus were relatively similar in body size, and because of the greater ability to interpret and compare counts with those of other populations.

The prevalence of nevi with a diameter of at least 2 mm was low. Therefore, data for nevi of at least 2 mm are presented as the proportion of the children with 1 or more nevi of at least 2 mm in diameter rather than as medians. To demonstrate the sex difference in nevus counts on the posterior neck (which is considered chronically exposed for boys and intermittently exposed for girls), we report the proportion of children with any nevus on the posterior neck by sex for each year. We used χ^2 tests to compare proportions across groups. All statistical tests were 2 sided, and statistical procedures were implemented using commercially available software (SPSS, version 15.0 for Windows; SPSS, Inc, Chicago, Illinois).

SENSITIVITY ANALYSIS

To verify the validity of pooling children recruited at different times and from different sources, we conducted sensitivity analyses as follows. First, we repeated the major analyses reported in this article on the 57 non-Hispanic white children who attended all 6 years of examinations (2001-2006). Second, we compared subject characteristics and nevus counts for the following 3 subsamples of non-Hispanic white children in the 2006 data collection: (1) children enrolled in 1998 from the MCO (n=150); (2) children from the same MCO enrolled in 2003 through 2004 (n=155); and (3) children enrolled from private pediatric practices and community settings in 2003 through 2004 (n=423). To validate the inclusion of intervention and control group children in this analysis of the natural history of nevus development, we compared nevus counts in 2006 for children randomly assigned to the 2 study groups.

RESULTS

Table 1 and **Table 2** provide characteristics of the study participants for each study year. Race/ethnicity is presented for all participants; additional characteristics are presented only for non-Hispanic white participants. **Figure 1** shows the median number of nevi over time by race/ethnicity. Non-Hispanic white children consistently exhibited a higher number of nevi compared with other racial/ethnic groups, and the differences increased as the children aged. Black children had the fewest nevi, followed by Asian/Pacific Islander children and Hispanic white children. The differences between non-Hispanic white children and all other groups became statistically significant at 5 years of age and increased in statistical significance from that point forward. Because non-Hispanic white subjects are known to have a 6- to 25-fold higher incidence of malignant melanoma compared with other racial/ethnic groups,[1] the remainder of the analysis focuses solely on the non-Hispanic white children.

Table 1. Characteristics (Categorical) of Study Participants Born in 1998 by Age[a]

Characteristic	3 (2001) (n=281)	4 (2002) (n=137)	5 (2003) (n=284)	6 (2004) (n=856)	7 (2005) (n=870)	8 (2006) (n=860)
	Age, y (Study Year)					
All Participants						
Race/ethnicity						
Non-Hispanic white	232 (83.8)	121 (89.6)	229 (81.8)	720 (84.6)	733 (84.5)	728 (84.8)
Hispanic white	29 (10.5)	9 (6.7)	38 (13.6)	80 (9.4)	78 (9.0)	78 (9.1)
Black	6 (2.2)	1 (0.7)	6 (2.1)	21 (2.5)	24 (2.8)	22 (2.6)
Asian/Pacific Islander	9 (3.2)	4 (3.0)	5 (1.8)	26 (3.1)	27 (3.1)	24 (2.8)
Native American	1 (0.4)	0	2 (0.7)	4 (0.5)	5 (0.6)	6 (0.7)
No. of other/missing[b]	4	2	4	5	3	2
Non-Hispanic White Participants						
	3 (2001) (n=232)	4 (2002) (n=121)	5 (2003) (n=229)	6 (2004) (n=720)	7 (2005) (n=733)	8 (2006) (n=728)
Sex						
Male	115 (49.6)	54 (44.6)	107 (46.7)	350 (48.6)	346 (47.2)	338 (46.4)
Female	117 (50.4)	67 (55.4)	122 (53.3)	370 (51.4)	387 (52.8)	390 (53.6)
Hair color						
Blonde	69 (29.9)	21 (17.4)	55 (24.1)	133 (18.6)	49 (6.7)	68 (9.4)
Red	11 (4.8)	7 (5.8)	7 (3.1)	27 (3.8)	25 (3.4)	34 (4.7)
Light brown	98 (42.4)	64 (52.9)	89 (39.0)	322 (45.0)	351 (48.0)	295 (40.6)
Medium brown	48 (20.8)	29 (24.0)	74 (32.5)	229 (32.0)	302 (41.3)	327 (45.0)
Dark brown/black	5 (2.2)	0	3 (1.3)	4 (0.6)	5 (0.7)	3 (0.4)
No. missing[b]	1	0	1	5	1	1
Eye color						
Blue/green	144 (62.3)	59 (48.8)	132 (57.9)	389 (54.5)	401 (54.8)	370 (50.9)
Brown/black	57 (24.7)	30 (24.8)	56 (24.6)	172 (24.1)	186 (25.4)	192 (26.4)
Hazel	30 (13.0)	32 (26.4)	40 (17.5)	153 (21.4)	145 (19.8)	165 (22.7)
No. missing[b]	1	0	1	6	1	1
Freckling						
Face, any	38 (16.4)	37 (30.6)	91 (39.7)	349 (48.5)	446 (60.8)	509 (69.9)
Arms, any	1 (0.4)	1 (0.8)	2 (0.9)	10 (1.4)	38 (5.2)	82 (11.3)
Back, any	0	0	3 (1.3)	9 (1.2)	29 (4.0)	52 (7.1)

[a] Unless otherwise indicated, data are expressed as number (percentage) of participants. Because of rounding, percentages may not total 100.
[b] Percentages are calculated exclusive of children with an "other" designation and/or missing data.

Table 2. Characteristics (Continuous) of Non-Hispanic White Study Participants Born in 1998 by Age

	Age, y (Study Year)											
	3 (2001) (n=232)		4 (2002) (n=121)		5 (2003) (n=229)		6 (2004) (n=720)		7 (2005) (n=733)		8 (2006) (n=728)	
Characteristic	No. of Children	Value	No. of Children	Value	No. of Children	Value	No. of Children	Value	No. of Children	Value	No. of Children	Value
Mean base skin color, b dimension[a]	232	11.1	121	11.3	227	10.4	717	11.0	732	10.8	723	10.9
Mean tanning score, b dimension[a]	231	2.3	121	1.9	227	1.8	717	2.8	732	2.7	723	2.6
Nevi												
Mean No. (SD)	231	6.2 (4.1)	121	11.8 (6.5)	229	19.3 (11.4)	719	21.8 (13.6)	732	28.8 (17.4)	728	31.6 (18.4)
Median No. (IQR)	231	6.0 (6.0)	121	11.0 (8.5)	229	17.0 (14.0)	719	19.0 (17.0)	732	25.0 (22.0)	728	29.0 (22.0)
Range	231	0-22	121	1-35	229	1-66	719	1-92	732	2-116	728	2-118
Mean height, cm	231	95.0	121	103.4	229	114.3	715	118.4	732	126.5	727	129.5
Mean weight, kg	231	14.4	121	16.3	229	20.0	718	21.6	732	24.2	727	27.3
Age range at time of examination, mo	231	33-41	121	45-53	229	61-75	719	69-81	732	81-93	727	93-105

Abbreviation: IQR, interquartile range.
[a] Skin color and tanning assessed by colorimetry using b dimension of the L a b system.

For all study years, our samples were approximately evenly split by sex (Table 1). The proportion of children with hair designated as blonde decreased with time, whereas the proportion with medium brown hair increased. This most likely reflects the natural darkening of hair during childhood rather than a change in the children included in each year's sample. About half of the children had blue or green eyes. Freckling was relatively infrequent at 3 years of age and increased steadily over time. By 8 years of age, 69.9% of the children had facial freckling, 11.3% had arm freckling, and 7.1% had back freckling. Base skin color, which ranged from 10.4

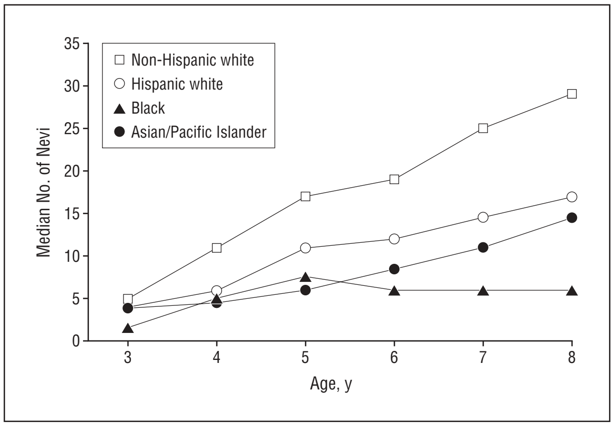

Figure 1. Median total numbers of nevi by race/ethnicity among children aged 3 to 8 years in Colorado at the 2006 examination. The distribution of nevi among non-Hispanic white children was significantly different from that in the other groups at 3 ($P = .03$), 4 ($P = .05$), 5 ($P = .001$), and 6 to 8 ($P < .001$) years of age (Kruskal-Wallis test for all comparisons).

to 11.3 on the b dimension, confirms that the samples for each of the years were fairly consistent in pigmentation (Table 2). The tanning score was lower for 2003, when the examinations were conducted in winter instead of summer (1.8 compared with 2.6-2.8 for later years). At 3 years of age, children had a median of 6 nevi. The median number of nevi increased by 4 to 6 per year, with the exception of the time from 5 to 6 years of age, when a median of only 2 new nevi were gained; however, examinations were completed only about 7 months apart for that period (Table 2).

Figure 2 shows increases in the numbers of nevi over time for all nevi, small nevi (<2 mm in diameter), larger nevi (≥2 mm in diameter), nevi in chronically exposed body parts, and nevi in intermittently or rarely exposed body parts. The total number of nevi was significantly higher for boys compared with girls starting at 6 years of age, at which point there was a median difference of 4 nevi ($P = .002$), with the difference growing to 5 nevi by 8 years of age ($P = .001$) (Figure 2A). The sex difference is primarily due to small nevi (<2 mm) (Figure 2D) and nevi in chronically exposed body parts (Figure 2B). By 6 years of age, boys had a median of 4 more small nevi (whole body) (Figure 2A) and 3 more nevi (any size) on their chronically exposed body parts (Figure 2B) compared with girls ($P = .001$ and $P < .001$, respectively). These sex differences do not appear to exist for larger nevi (≥2 mm) (Figure 2E) or for intermittently exposed body parts (Figure 2C). The sex difference with regard to chronically exposed body parts is further demonstrated for the posterior neck, which is considered chronically exposed for boys and intermittently exposed for girls (Figure 2F). Although the absolute counts of nevi on the posterior neck were small, at least twice as many boys were found to have any nevi on their posterior neck compared with girls at all ages studied (all, $P < .05$). The number of children with any nevi on the posterior neck appears to have leveled off for both sexes by about 6 years of age. The sex difference in nevi cannot be explained by greater body size; at 8 years of age, the boys were only 4% heavier and 2% taller than the girls (Table 2).

SENSITIVITY ANALYSIS

Fifty-seven non-Hispanic white children attended all 6 skin examination sessions (2001-2006). To investigate whether the addition of children in the 2003-2004 recruitment could have substantially altered the trends reported in the main analysis, plots of all nevi, nevi in chronically exposed body sites, nevi in intermittently exposed body sites, and nevi of less than 2 mm in diameter were constructed (data not shown). All patterns presented in Figure 2 were replicated, including the sex difference for nevi in chronically exposed body sites beginning at 6 years of age, lack of a sex difference for intermittently exposed body sites, and the sex difference in nevi of less than 2 mm, although this difference emerged at 7 rather than 6 years of age in this subset of subjects.

Subject characteristics and nevus counts at 8 years of age were compared for children from 3 recruitment samples. The 3 samples were statistically similar ($P > .20$) for freckling, hair color, sex, base skin color (b dimension), height, and weight. Marginally significant differences were found for eye color (a higher proportion of children recruited from the MCO in 2003-2004 had blue or green eyes and fewer had hazel eyes compared with the other subsamples [$P = .09$]), all nevi (children recruited from the MCO at both times had somewhat fewer nevi than children recruited from other locations [$P = .18$]), and tanning (children recruited from the MCO in 1998 had somewhat higher tanning scores compared with other children [$P = .18$]). Statistically significant differences were found for nevi at least 2 mm in diameter and for nevi in intermittently exposed sites. Children recruited from private practices and community locations had a median of 2 nevi of at least 2 mm in diameter compared with medians of 1 nevus for both MCO samples ($P = .02$). Children from private practices and community locations had a median of 21 nevi in intermittently exposed sites compared with medians of 18 for both MCO samples of children ($P = .04$). In general, intervention group status was not related to the number of nevi. There was no statistically significant difference for all nevi, nevi of at least 2 mm, and nevi in intermittent and chronically exposed sites. The Mann-Whitney test showed a significant difference for nevi with a diameter of less than 2 mm, with children randomly assigned to the control group having fewer nevi (control group median, 23; intervention group median, 26 [$P = .04$]). Because the intervention was intended to decrease UV exposure, it was expected that the intervention would be associated with fewer rather than more nevi.

COMMENT

Non-Hispanic white children in Colorado developed approximately 4 to 6 new nevi per year on average from 3 to 8 years of age. Most of these nevi (90%-95%) remained smaller than 2 mm in diameter through 8 years of age. The accumulation of nevi was comparable for boys and girls when nevi in intermittently exposed body sites were considered. However, in chronically exposed areas (the face, front of the neck, and lower outer arms for both

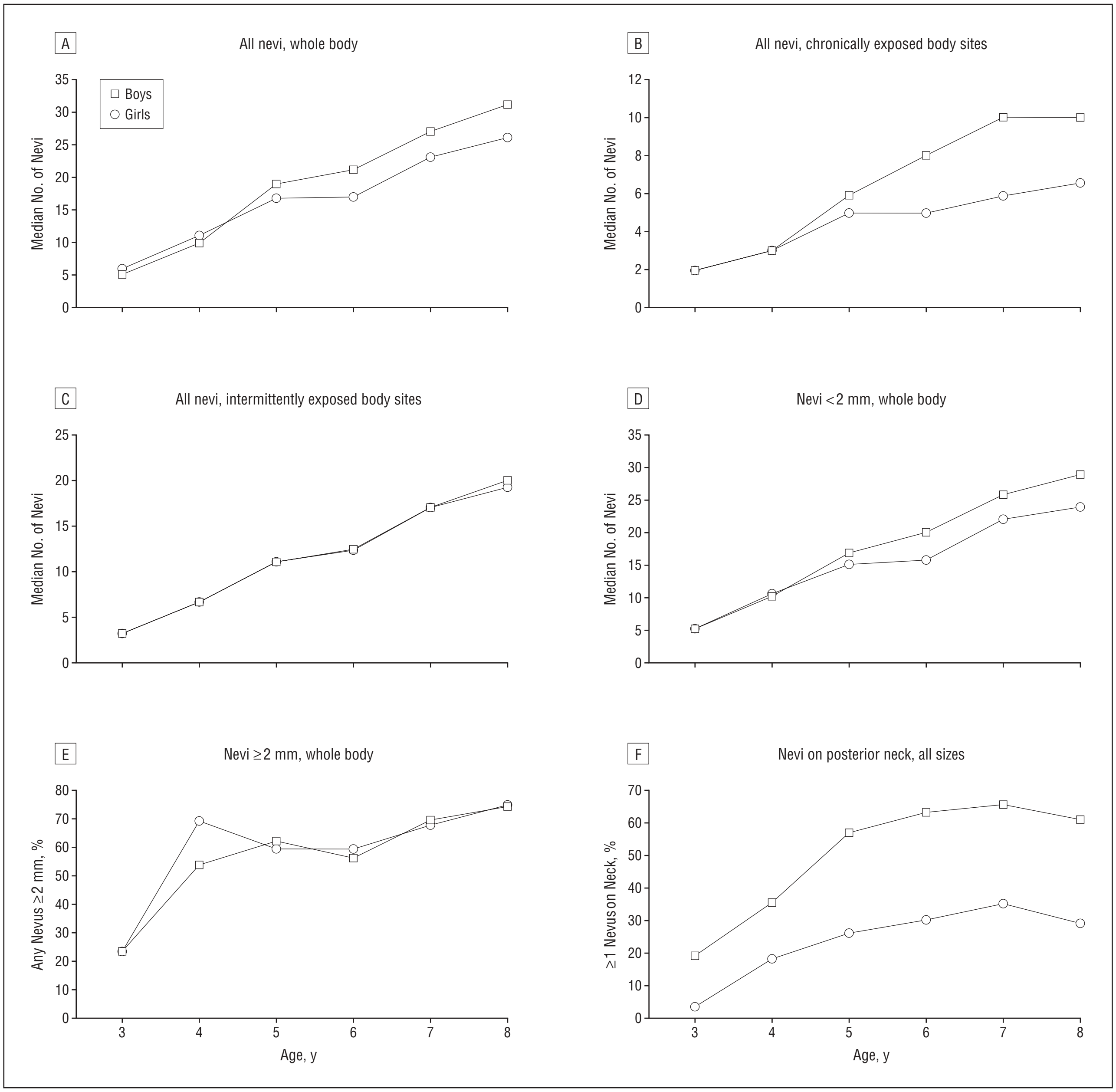

Figure 2. Median total numbers of nevi on the whole body (A), all nevi on chronically exposed parts (B), all nevi on intermittently exposed parts (C), nevi of less than 2 mm in diameter on the whole body (D), nevi of at least 2 mm in diameter on the whole body (E), and all nevi on the posterior neck (F) by sex among non-Hispanic white children aged 3 to 8 years in Colorado during the 2001-2006 study period. A, Boys were significantly different from girls at 6, 7, and 8 years of age ($P<.02$). B, Boys were significantly different from girls at 5, 6, 7, and 8 years of age ($P\leq.001$). C, Boys and girls were statistically similar. D, Boys were significantly different from girls at 6, 7, and 8 years of age ($P\leq.01$). E, Boys and girls were statistically similar. F, Boys were significantly different from girls at 3, 5, 6, 7, and 8 years of age ($P<.001$) and less so at 4 years of age ($P=.03$). All statistical analyses were performed using the Mann-Whitney test.

sexes, and the back of the neck in boys), there was a divergence between the sexes starting at about 5 years of age, with boys accumulating more nevi in the chronically exposed areas. By 8 years of age, boys had about 20% more total nevi than girls and about 50% more nevi in chronically exposed areas. The greater number of nevi in chronically exposed areas for boys was only minimally a result of greater numbers on the posterior neck, which is considered to be chronically exposed for boys but not girls. The data suggest that the number of nevi on chronically exposed sites began to level off for both sexes at 7 to 8 years of age. Our study verifies the considerably higher number of nevi on non-Hispanic white children compared with other groups,[17] which mirrors the differences in melanoma incidence by race/ethnicity.[1] The sensitivity analysis supports the conclusion that the overall trends found were not affected by the inclusion of children from 3 different sampling sources. The inclusion of children from private pediatric practices and community sites may have resulted in slightly increased counts for nevi of at least 2 mm and for nevi in intermittently exposed body sites.

The sex difference in nevi that we found in our study population has been noted by researchers studying nevi in other parts of the world, although our finding that the sex difference in nevi is limited to chronically exposed body areas differs from findings from other regions. Autier et al[18] examined children aged 6 to 7 years in 4 European cities and found that boys had slightly more nevi compared with girls and that the excess nevi in boys was predominantly due to nevi on the head, neck, trunk, and shoulders. Although the head and neck are chronically exposed, the trunk and shoulders are generally not considered chronically exposed. Darlington et al[11] studied Australian adolescents from the time they were 12 to 13 years of age until they were 16 to 17 years of age and found sex differences for chronically (face and neck) and intermittently exposed areas (shoulder and back). Their study provides evidence of a saturation level for the face and neck reached at 14 to 15 years of age for both sexes, with boys topping off at significantly higher counts than girls. Children in that study continued to accumulate nevi on the shoulders and back throughout the study. In a separate analysis of children in our study, we found that the number of nevi on the face was not associated with sunburns to the face, whereas the number of nevi on the back was associated with sunburns to the back.[8] This also supports the saturation hypothesis: the faces of our children showed evidence of saturation, whereas the backs of our children did not. However, continuing to follow up our cohort into the adolescent years could show that there are multiple periods of plateau in nevus development, followed by periods of increase. These could be owing to developmental biology, age-related periods of greater sun exposure, or a combination of these 2 factors.

In our Colorado cohort, we found that the sex difference for chronically exposed body sites emerged at approximately 6 years of age. In the United Kingdom, Pope et al[7] also observed the emergence of a sex difference at 6 years of age. The fact that the sex difference in Colorado children is limited to chronically exposed body parts suggests that sun exposure plays a key role. This difference could be due to sun exposure alone, or it could be due to an interaction between sun exposure and a biological predisposition of boys to develop more nevi.[18] However, there has been no biological mechanism proposed for this sex difference. It has been suggested that there is a delay of 2 years or more between sun exposure and resultant nevus development.[19] If the sex difference we observed is due to sun exposure alone, our findings suggest that parents protect their very young male and female children equally from sun exposure until 3 to 4 years of age, at which time parents may become more diligent about the sun protection of their female children compared with their male children, and the subsequent effect on nevus development becomes apparent at 6 years of age. The sex difference in nevi may also be influenced by sex differences in childhood activities. Boys may be more involved in outdoor sports and other outdoor activities. There may also be sex differences in clothing styles that lead to the divergence in the number of nevi, although the pattern of nevus development suggests that both boys and girls get their highest levels of exposure on the lower outer arms and the face and neck. Sun protection studies have shown that boys use less sun protection than girls,[20-23] and the pattern of nevus emergence in our cohort, as well as the divergence as early as 6 years of age, suggest that this sex-based behavioral difference starts young when the behavior is still in the control of parents rather than children.

Nevi in our cohort of Colorado children were mostly smaller than 2 mm in diameter. Studies in other regions have found considerably higher levels of larger nevi ($\geq$2 mm), and in many cases studies have not even counted nevi of less than 2 mm.[4,23-25] For example, in a study of children in Estonia by Kallas et al,[23] those aged 9 years had a median of 26 nevi of at least 2 mm in diameter. Some portion of these differences in findings may be rooted in study methods. We considered nevi to be at least 2 mm only if they completely filled the 2-mm cutout in the measurement stencil. Some studies[11,25] have considered nevi to be at least 2 mm if any dimension of the nevus is at least 2 mm. Because many of the nevi measured in our study population were close to 2 mm in diameter, we expect that as the cohort ages those nevi will grow and the apparent differences in nevus size between our cohort and those of other studies will diminish. However, sun exposure patterns and clothing norms in Colorado may lead to a different pattern of nevus development. Autier et al[26] suggested that genetically determined characteristics (ie, skin type and eye color) play a major role in development of smaller nevi ($<$5 mm) but that intense sun exposure (such as that resulting in sunburns) is necessary for the development of large nevi ($>$5 mm). Bauer et al,[5] however, suggested that intermittent and chronic sun exposure are important in the development of nevi, with intermittent intense exposure being relatively more important in regions of higher latitude and chronic exposure being more important in regions of lower latitude.

Compared with our Colorado cohort, studies of similarly aged children in Vancouver, British Columbia,[9] Bochum, Germany,[4] and Brisbane, Australia,[24] have reported higher total nevus counts, whereas studies in Hamburg, Germany,[27]; Ramat-Gan/Jerusalem, Israel,[28] and Kaunas, Lithuania,[10] have reported lower counts. Two separate English studies, one in the West Midlands[7] and the other in Oxford,[29] reported counts very similar to ours in Colorado. Sun exposure (at home and on vacation), behavioral patterns, and genetic variability are likely to contribute to regional differences in nevus development. Colorado has more than 300 sunny days a year and most of the population lives at an elevation above 5000 ft. Furthermore, the non-Hispanic white population of Colorado may have greater genetic diversity affecting pigmentation and nevus development than the populations in some other regions previously studied.

Our study has some limitations. Our sample was not randomly selected from the population and therefore may not be representative of the larger population. Most likely, the study attracts participation from families that are more aware of and/or concerned about skin cancer. Thus, families in our study may be more vigilant about sun protection and, if so, our study might underestimate nevus prevalence in non-Hispanic white Colorado children. The lower participation rates in skin examinations in 2001 and 2002, which are most likely owing to the lack of a financial incentive in those years, may have resulted in further bias toward the inclusion of children with parents who are more concerned about skin cancer. This bias, if present, could have resulted in greater underestimation of nevi in the first 2 years compared with later years if these families were more diligent about sun protection; thus, the children developed fewer nevi than other children. Low participation in 2003 was due to delayed recruitment and is not likely to have produced bias in a particular direction. The net effect of the potential bias could have resulted in the appearance of a more dramatic increase in nevus counts from the earlier years (2001-2002) to the later years (2003-2006) than what would have been found in a more representative sample. Despite potential bias in participation that may have differentially affected nevus estimates by year, the comparisons of brown/black eye color (Table 1) and base skin color (Table 2) indicate that the samples across all years were similar phenotypically.

A portion of our study population received a sun protection intervention designed to reduce sun exposure that could have resulted in the prevention of nevus development. However, our analysis generally showed no effect of the intervention on nevus counts, with the exception of nevi smaller than 2 mm in diameter, for which the analysis showed lower nevus counts for the control group, contrary to the intention of the intervention.

Rather than following up a single sample of children recruited shortly after birth in 1998, our study combined samples recruited in 1998 and in 2003 through 2004, with all children being from the same 1998 birth cohort. This could call into question whether our treatment of the 2 samples as a single cohort for analysis is appropriate. However, our sensitivity analysis showed that inclusion of the 2 samples strengthens the study by including a larger number of children and somewhat greater variation in the children studied (eg, children recruited from private practices and community sites in 2003-2004 tended toward development of higher numbers of nevi). Thus, the inclusion of the additional sample of children strengthens the ability to generalize the findings to all Colorado non-Hispanic white children born in 1998.

Except for 2003, when data collection was later in the year because of delayed funding, all data collection occurred during the summer months. Therefore, we are unable to examine the seasonality of nevus development. For example, an interesting question is whether nevi tend to develop during seasons of high sun exposure or whether they develop some months after sun exposure (eg, in the winter). Seasonal trends have been detected in melanoma incidence, with more melanomas being detected in the spring and summer months.[30] Because the skin examinations occurred at approximately annual intervals, our data cannot be used to address this issue.

In conclusion, this study contributes to the body of literature on nevus development in children by adding the first annual longitudinal study in children before 10 years of age and the first US study. Children in Colorado exhibit nevus development patterns similar to those in the United Kingdom but notably different from children in other Northern European countries and Australia, particularly with respect to the size of nevi and the patterns of nevus development between intermittently and chronically exposed body sites. These differences highlight the importance of studying nevus development in various regions of the world where sun exposure patterns and behavioral norms vary; such studies can aid in the understanding of the complicated relationship between nevus development and malignant melanoma.

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