Effect of hair color and sun sensitivity on nevus counts in white children in Colorado

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Background: It has been widely reported that individuals with a light phenotype (ie, light hair color, light base skin color, and propensity to burn) have more nevi and are at greater risk for developing skin cancer. No studies have systematically investigated how phenotypic traits may interact in relation to nevus development.

Objective: We sought to systematically examine whether any combinations of phenotype are associated with a greater or lesser risk for nevus development in white children.

Methods: In the summer of 2007, 654 children were examined to determine full body nevus counts, skin color by colorimetry, and hair and eye color by comparison with charts. Interviews of parents were conducted to capture sun sensitivity, sun exposure, and sun protection practices.

Results: Among 9-year-old children with sun sensitivity rating type II (painful burn/light tan), those with light hair had lower nevus counts than did those with dark hair (*P* value for interaction = .03). This relationship was independent of eye color, presence of freckling, sex, usual daily sun exposure, sunburn in 2004 to 2007, sun protection index, and waterside vacation sun exposure. The difference in nevus counts was further determined to be specific to small nevi (<2 mm) and nevi in intermittently exposed body sites.

Limitations: Geographic and genetic differences in other study populations may produce different results.

Conclusion: The standard acceptance that dark phenotype is a marker for low melanoma risk and light phenotype a marker for high risk may need to be reevaluated. In non-Hispanic white children, dark-haired individuals who burn readily and then tan slightly are more prone to nevus development, and may therefore be a previously underrecognized high-risk group for melanoma. (J Am Acad Dermatol 2010;63:430-9.)

Key words: children; epidemiology; hair color; interaction; nevus; phenotype; sun sensitivity.

In 2008, more than 62,480 new melanomas were diagnosed in the United States, and there were more than 8000 deaths.[1] The latest national data based on cases diagnosed in 2008 place melanoma sixth in incidence among all cancers for men and seventh for women.[2] Based on rates from 2003 to 2005, 1.8% (or 1 in 55) of men and women born today will be given a diagnosis of melanoma at some time during their lifetime.[3]

Melanoma incidence is highest in whites, up to 20 times higher than for other racial or ethnic groups, and is strongly associated with the presence of numerous melanocytic nevi.[4,5] The total number of nevi on the whole body is thought to be the most important independent risk factor and the risk of melanoma increases almost linearly with rising numbers of nevi.[6] The role of benign melanocytic nevi as precursors and not only as risk markers for the development of melanoma is controversial.[7] A history of a pre-existing nevus at the site of a melanoma is recorded in between 19%[8] and 85%[9] of cases. A more recent histopathological analysis of melanomas by Skender-Kalnenas et al[7] suggests that greater

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than 50% of melanomas are associated with melanocytic nevi either of the benign or atypical type. In addition, the presence of numerous nevi and melanoma share several common risk factors (eg, light skin, light hair, light eyes, inability to tan, history of sunburns).[10-19] Nevi are therefore considered reasonable markers for estimating melanoma risk.

The study of melanocytic nevi in young children is important for skin cancer prevention efforts because childhood is a time when nevi are acquired rapidly.[12] Although children are rarely given the diagnosis of melanoma, the number of nevi in childhood is often used as a proxy in determining their melanoma risk.

Many studies have reported that children who are of a lighter phenotype acquire more nevi, even when adjusting for factors such as sunburn history and sex.[13,17,19-23] However, none of the previous studies that have investigated the relationship between phenotype and childhood nevus development systematically analyzed whether the 5 major phenotypic factors (freckling, hair color, eye color, base skin color, and sun sensitivity) interact in relation to nevus development. Studies have usually focused on the main effects of phenotype on nevus development and only occasionally report interaction effects as incidental findings.[13,18,24-26] In a recent study by our group,[26] we found that very light-skinned children who tan had more nevi than those who did not tan, whereas in darker-skinned white children the relationship between tanning and nevi was not present. This suggests that the relationship between sun exposure and nevus development is modified by degrees of skin color.

The present analysis was motivated by the clinical observation of our team of skin examiners, over the past 5 years, of a subset of blonde children who appeared to tan readily and had low numbers of nevi. This suggested there is a subset of children who do not conform to the expectation that light hair color is associated with an inability to tan and higher nevus counts. These observations led us to believe that the relationship between these phenotypic characteristics and nevus development may not be as straightforward as generally assumed. We hypothesized that, by systematically testing interaction terms involving phenotypic traits, we would identify modifying effects on nevus formation involving skin sun sensitivity, hair color, and skin color, among non-Hispanic white children. Freckling and eye color were initially included in this hypothesis, but insufficient numbers of study participants representing variations of freckling and eye color within categories of these 3 main phenotypic traits precluded their systematic evaluation.

CAPSULE SUMMARY

- Studies have indicated that individuals with a light phenotype have more nevi and are at increased risk for melanoma.
- Among 9-year-old children with type II skin (burn readily and tan lightly), we found those with dark hair had significantly more nevi compared with those with light hair.
- A clearer understanding of how phenotype relates to nevus development and melanoma could lead to individualized primary and secondary prevention recommendations that may reduce melanoma incidence and mortality.

METHODS

Study design and sample

The study population analyzed was part of a nested randomized controlled trial within a prospective cohort study. Longitudinal data on phenotypic characteristics, sun exposure, and nevus counts were obtained from a cohort of children in Colorado starting at age 6 years and continuing through age 9 years.[22] The participants were children born between January and September 1998, recruited from private pediatric practices and a large managed care organization in the Denver metropolitan area.[19,22] Children were excluded if they had a debilitating condition or if their parents could not speak English. The majority of the children (86.5%) lived in Colorado since birth. This study was reviewed and approved by the Colorado Multiple Institutional Review Board.

For this analysis, we included only those children who had a skin examination in 2007 (age 9 years), the most current and complete data set available for analysis (n = 850). We excluded redheads (n = 38) because they are known to have fewer nevi than those with other hair colors, suggesting that the development of nevi in red-haired children is fundamentally different,[15,27] possibly because of polymorphisms in the melanocortin 1 receptor (*MC1R)* gene.[28] Children with a parent-reported race/ethnicity designation of Hispanic, African American/black, Asian/Pacific Islander, Native American, and unknown (n = 158) were excluded because these populations have been shown to have fewer nevus counts overall[22] and have a considerably lower melanoma risk.[29]

Skin examination

Skin examinations in 2007 were conducted by a team of 7 dermatologists, pediatricians, pediatric nurses, and nurse practitioners during the summer

months (June-early September) to allow for observation of summer tanning. Skin examinations provided full body melanocytic nevus counts (excluding the genitals and scalp). Nevi were differentiated from freckles and café-au-lait macules by whether or not they were raised (because only nevi are raised) and if flat, by the fact that early junctional nevi are dark brown, have regular edges, and do not occur in patches as do freckles.[13] Warts were distinguished from nevi by their verrucous nature.[13] Congenital nevi were excluded from total nevus counts. Plastic stencils were used to measure nevus size. Nevi were recorded as being either raised or flat, and coded by size: less than 2 mm, greater than or equal to 2 mm to less than 5 mm, or greater than or equal to 5 mm. Placement of nevi was recorded on a body map[13]; this information was used to classify nevi as residing on "intermittently" or "chronically" sun-exposed body sites. Before the beginning of the 2007 data collection period, nevus counting protocols were reviewed as part of skin examination retraining sessions conducted by the lead study dermatologist (J. G. M.). Over the duration of the data collection period, 53 children were evaluated separately by two different examiners to allow determination of interrater reliability and to allow any discrepancies in procedures to be corrected. All examiners participated in the duplicate examinations. Using a 2-way analysis of variance mixed effects model, the interrater reliability coefficient was calculated to be 0.88.

Phenotype of the subjects was assessed in part by visual examination. Eye color was recorded (blue, green, hazel, light brown, or dark brown), and for analysis was dichotomized based on similar mean nevus counts as "light" (blue, green, hazel) or "dark" (light or dark brown). Hair color was assessed using hair dye samples and dichotomized as "light" (blonde, light brown) or "dark" (medium or dark brown, black) based on precedence in the literature.[30] Freckling was assessed by means of a diagram with pictures of various freckling patterns on the face, back/shoulders, and outside of arms.[13] Examiners recorded the picture that best represented the freckling pattern of each child. For analysis, freckling was dichotomized as "any" versus "none." Skin coloration was measured using a Chroma Meter CR-400 (Konica Minolta Sensing Americas Inc, Ramsey, NJ). The Chroma Meter CR-400 measures across the visible light spectrum using the three dimensional Hunter Lab color scale. The L scale represents the color spectrum from total black to total white. Increasing values on the L scale (more white) are indicative of lighter skin color.[31,32] To obtain an inner arm measurement representing base skin color, a ruler was placed with the zero mark in the center of the child's axilla. Five readings were taken at a point 7.5 cm below the axilla. To qualify as light skinned, the average L reading was greater than or equal to 60 L units. Thus for analysis, base skin color was dichotomized as "light" ($\geq$60 L) and "dark" (<60L). This cut-point was determined by consensus of a team of dermatologists and investigators.[26]

Surveys

Risk factors for nevus development, including sun exposure history, sunburns, and a sun sensitivity rating similar to the Fitzpatrick score,[33] were reported by parents each summer from 2004 to 2007 when recall of sun exposures was expected to be optimal. Trained interviewers conducted the interviews by telephone with the parent or guardian who was the child's primary caregiver. The survey response rates for 2004 to 2007 among the subset of study participants eligible for this analysis were 96%, 98%, 99%, and 98%, respectively.

Usual daily summer sun exposure was assessed using the composite of two variables from each interview year from 2004 to 2007: the number of days per week in the summer the child typically spent more than 15 minutes outside between 11:00 AM and 3:00 PM, and the usual number of hours spent outside during these occasions. These variables were multiplied to create a single variable for each year representing the total number of hours outside per week between 11:00 AM and 3:00 PM. The 4 resulting variables were averaged and dichotomized as 0 to 14 h/wk ("half-time or less") versus 15 to 28 h/wk ("most-all the time"). The number of sunny waterside vacations taken between birth and age 8 years was collected through questions asked each year about vacations to sunny locations. "Waterside" locations were defined as destinations known to be associated with recreational activities such as swimming, surfing, waterskiing, and boating.[34] Vacations to these locations were only included if they occurred during a season in which outdoor water activities would be expected to occur.[34] We analyzed number of sunny waterside vacations through age 8 years instead of age 9 years because in a previous analysis, we found a lag of at least 1 year in the relationship between vacation sun exposure and nevus development.[34] The number of waterside vacations was used as a continuous variable in multivariate analysis. A sun protection index was created for each year by taking the mean of 4 variables assessing the frequency of using sunscreen, shade, clothes covering most of the body, and hats (5 = all of the time, 4 = most of the time, 3 = about half the time, 2 = not very often, 1 = never) while outside between 11:00 AM and

3:00 PM for more than 15 minutes. Index scores for the 4 years were averaged and a score of 3.5 or above was considered "high sun protection," whereas a score below 3.5 was considered "low sun protection." Sun sensitivity was assessed in 2007 by the following question: "If your child were outside in strong sunshine at the beginning of the summer for 1 hour with no protection, which statement describes what would happen?" The sun sensitivity skin ratings were read to the respondent as possible answer choices categorizing the degree of sunburn the following day relative to the degree of tan 1 week later: painful/none (type I), painful/light (type II), slight/little (type III), or none/good (type IV). Sunburns were assessed annually by a question asking whether the child experienced any sunburn in the past year that caused reddening of the skin lasting until the next day regardless of severity. The resulting information was used to create a dichotomous variable: "any burn" in the previous 4 years versus "no burn."

Data analysis

Based on our hypothesis that phenotypic traits may interact in relation to nevus development, we began our analysis with 5 phenotype main effect variables (presence of freckling [any/none], hair color [light/dark], eye color [light/dark], base skin color [light/dark], and sun sensitivity scores [types I-IV]). A 5-way table was created that included all variables to assess adequate cell size for each phenotypic combination. Presence of freckling and eye color had several cells with low numbers, prohibiting their inclusion in further analyses. For example, for children with no freckles, light hair, dark skin, and sun sensitivity type I, the cell counts for both eye colors (light and dark) were less than 5. Hair color, skin color, and sun sensitivity were retained and we confirmed that all remaining cells had sufficient numbers (≥ 5) to proceed with the analysis.

The second step in the analysis was to plot nevus counts by hair color, base skin color, and sun sensitivity rating to visualize the potential interactions between these variables. In Fig 1, the mean number of nevi is plotted by sun sensitivity rating, stratified by hair color. Fig 2 represents the mean number of nevi by sun sensitivity rating, stratified by base skin color. Fig 3 is the combination of Figs 1 and 2, which is the number of nevi by sensitivity score, stratified by base skin color and hair color. The plots suggest that within sun sensitivity type II the relationships among hair color, base skin color, and mean number of nevi is modified. Therefore, we dichotomized sun sensitivity rating as type II versus all others (types I, III, IV).

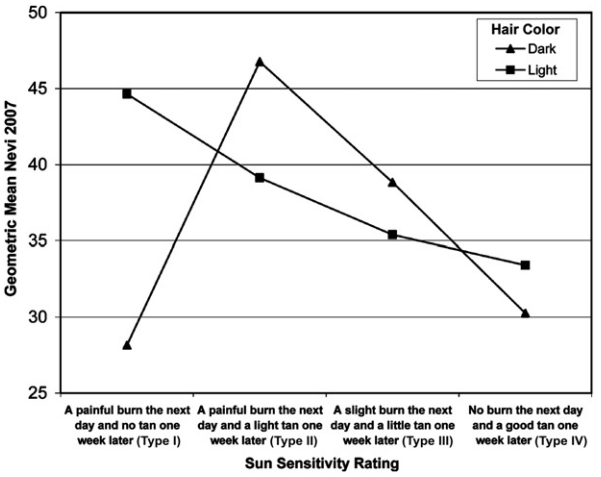

Fig 1. Mean number of nevi by sun sensitivity by hair color. Note: Y-axis begins at 25.

Interaction terms were created by coding the phenotypic traits of interest as 0 (reference: dark hair; dark skin; sun sensitivity types I, III, IV) versus 1 (light hair; light skin; sun sensitivity type II) and multiplying the values to create up to 3-way interaction terms (eg, light hair × light skin × type II).

The number of 2007 log-transformed total body nevus counts (all sizes, excluding scalp and genitals) was the main dependent variable. The choice to report geometric means of nevus counts (Table I) and to use log-transformed nevus counts in our multivariate analysis (Table II) resulted from the observation of a skewed distribution of the 2007 nevus counts and thereby recognizing the need to stabilize the data variance.[35]

To systematically test for interaction effects among the 3 main phenotypic variables, the 3 main effects and 3-way and 2-way interaction terms were included in the initial regression model.[35] Then, in a step-down backward approach, the 3-way interaction term was assessed first. If the 3-way interaction term was not revealed as statistically significant ($P < .05$), then all 2-way interaction terms were tested and those not significantly associated with nevus counts were removed from the model. To verify that the relationships between phenotype main effects or interaction terms and nevi were not a result of confounding, variables including waterside vacation sun exposure, usual daily sun exposure, sun protection index, sunburn in 2004 to 2007, and sex were controlled for in the multiple regression models. For interpretation, the antilog was used to convert multiple linear regression coefficients to the multiplicative factor by which nevus counts are expected to change, on average, for every one-unit increase in the predictor variable.

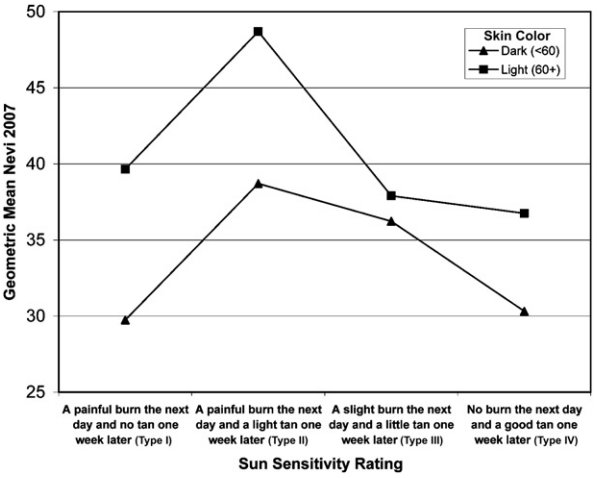

Fig 2. Mean number of nevi by sun sensitivity by base skin color. Note: Y-axis begins at 25.

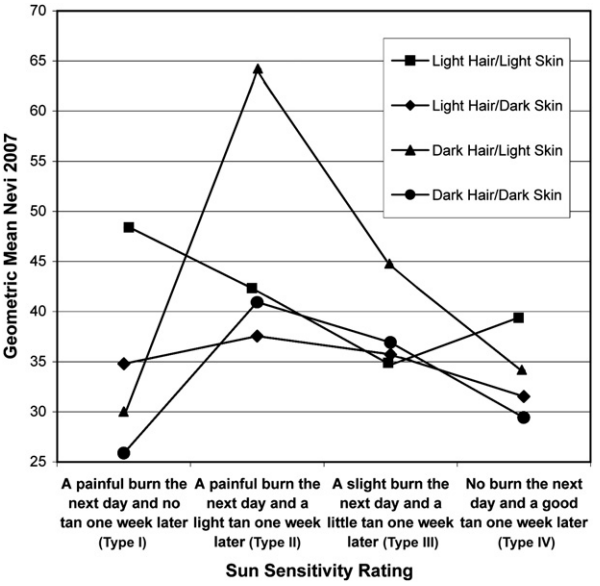

Fig 3. Mean number of nevi by sun sensitivity by hair color by base skin color. Note: Y-axis begins at 25.

To further investigate the relationship among hair color, skin color, sun sensitivity, and nevus counts, we repeated our analysis on 2007 log-transformed nevus counts less than 2 mm, greater than or equal to 2 mm, on chronically exposed body sites (defined as face, front of neck, outside of forearms, back of the hands, and, for boys only, the back of neck), and intermittently exposed body sites (defined as trunk, legs, upper sides of arms, inside of forearms, and, for girls only, back of neck).[22]

RESULTS

The cohort of children included in this study was relatively advantaged, as indicated by the education level of parents (76% of parents reported at least a college degree) and income (61% had annual incomes > $75,000) (Table I). As shown in Table I, children with a sun sensitivity type II had the highest mean nevus counts when compared with the other sun sensitivity ratings (type II: 41.7 vs type I: 36.3, type III: 36.7, and type IV: 31.7, $P = .002$). Light eye color, presence of freckling, light base skin color, sunburn in 2004 to 2007, and waterside vacation sun exposure were all significantly related to increased nevus counts (all $P < .05$). Boys also had more nevi, an average of 5 more compared with girls ($P < .001$). Hair color, sun protection index, usual daily sun exposure, household income, and parent education were not significantly related to nevus count.

Table II reports the final results of the multiple linear regression analysis examining interaction effects of the 3 phenotypic traits (hair color, skin color, sun sensitivity). The 3-way interaction (light hair × light skin × type II) was not significant and was removed from the model. Subsequently, the following 2-way interactions were sequentially removed because of lack of significance: light hair × light skin and type II × light skin (both $P > .05$). Only one 2-way interaction remained: light hair × type II (B = −0.23, $P = .03$). The antilog (B) transformation for this term (0.79) reveals that the simultaneous presence of both light hair and sun sensitivity type II is associated with 21% fewer nevi compared with all other combinations of these two factors. Other variables significant in the multivariate model include: waterside vacation sun exposure, sex, presence of freckling, and light eye color.

Replication of analysis by size and body location of nevi

Nevi measuring less than 2 mm represented 92% of the 2007 total nevus counts whereas nevi greater than or equal to 2 mm represented only 8%. Chronically exposed body sites contained 31% of the total nevus counts and intermittently exposed body sites contained 69%. The interaction term found to be a significant predictor of all nevi (light hair × type II) was found to be significantly associated with counts of nevi less than 2 mm (B = −0.26, $P = .02$), but not with counts of nevi greater than or equal to 2 mm (B = −0.17, $P = .55$). The interaction term was also significantly associated with nevi in intermittently sun-exposed body sites (B = −0.28, $P = .02$), but not with nevi in chronically exposed body sites (B = −0.18, $P = .14$).

DISCUSSION

Hair color modifies the relationship between sun sensitivity type II and nevus counts in white children in Colorado. For those with dark hair the mean

Table I. Whole body melanocytic nevus counts (in geometric means and 95% confidence intervals) by phenotype and demographic characteristics in white non-Hispanic Colorado children age 9 years, N = 654

Characteristic	n	%	Nevus count GM (95% CI)	*P* value*
Sex				
Male	304	46	39.4 (36.9-42.1)	<.001
Female	350	54	34.3 (32.1-36.6)	
Sun sensitivity†				
Painful burn/no tan (type I)	56	9	36.3 (29.8-44.3)	.002
Painful burn/light tan (type II)	167	26	41.7 (38.2-45.4)	
Slight burn/little tan (type III)	295	46	36.7 (34.3-39.3)	
No burn/good tan (type IV)	121	19	31.7 (28.4-35.2)	
Hair color				
Light (blonde, light brown)	378	58	36.5 (34.4-38.7)	.93
Dark (medium-dark brown, black)	276	42	36.7 (33.9-39.7)	
Eye color				
Light (blue, green, hazel)	482	74	38.4 (36.4-40.5)	<.001
Dark (brown)	172	26	32.0 (29.1-35.2)	
Presence of freckling‡				
Any	476	73	39.7 (37.6-41.9)	<.001
None	174	27	29.2 (26.7-31.9)	
Base skin color (L scale)§				
Light (≥60)	219	34	40.9 (37.6-44.4)	<.001
Dark (<60)	433	66	34.6 (32.8-36.6)	
Sun protection index//,¶				
High score (≥3.5)	88	13	35.7 (31.1-40.9)	.70
Low score (<3.5)	565	87	36.7 (34.9-38.5)	
Sunburn in 2004-2007				
Any burn	561	86	37.6 (35.7-39.5)	.007
No burn	93	14	31.2 (27.3-35.7)	
Usual daily sun exposure#				
Most-all the time	90	14	40.5 (36.4-45.0)	.09
Half time or less	564	86	36.0 (34.2-37.9)	
Waterside vacation sun exposure (Birth-8 y)				
≥1 Vacation	504	77	37.7 (35.8-39.8)	.02
None	150	23	32.9 (29.8-36.4)	
Household income**				
<$75,000	245	39	36.7 (34.1-39.5)	.52
$75,000-$99,999	178	28	35.2 (31.9-39.0)	
≥$100,000	208	33	37.9 (34.9-41.1)	
Parent education				
High school or less	41	6	43.6 (36.5-52.1)	.24
Some college	115	18	34.8 (33.7-40.5)	
College graduate	284	43	36.3 (33.6-39.1)	
Beyond college	214	33	36.7 (34.0-40.0)	

CI, Confidence interval; *GM*, geometric mean.
*P value based on analysis of variance of log-transformed nevus counts.
†Fifteen missing cases; Bonferroni analysis shows that type II is significantly different from type IV, $P = .001$.
‡Four missing cases.
§Two missing cases; measures skin reflectance, higher values indicate lighter skin color.
//One missing case.
¶Mean sun protection index from 2004-2007.
#Mean sun exposure from 2004-2007.
**Twenty-three missing cases.

number of nevi spiked at sun sensitivity type II, and for those with light hair color we saw a decrease in the mean number of nevi from types I to II and then a continued decrease in mean number of nevi in types III and IV (Fig 1). As shown, those with light hair and type II had considerably fewer nevi than those with dark hair and type II. The spike at type II for those with dark hair was an unexpected finding and is

Table II. Relationship among nevi, phenotype, sun exposure, and interaction terms in white non-Hispanic Colorado children age 9 years, N = 654, multivariate analysis

Predictor	B	SE	antilog (B)*	*P* value
Sex				
Female	−0.12	0.05	.88	.01
Male	ref			
Sun sensitivity				
Painful burn/light tan (type II)	0.29	0.09	1.34	<.001
All others (types I, III, IV)	ref			
Hair color				
Light (blonde, light brown)	0.01	0.05	1.01	.85
Dark (medium-dark brown, black)	ref			
Eye color				
Light (blue, green, hazel)	0.14	0.05	1.15	.01
Dark (brown)	ref			
Presence of freckling				
Any	0.25	0.05	1.28	<.001
None	ref			
Base skin color (L scale)†				
Light (≥60)	0.07	0.05	1.07	.17
Dark (<60)	ref			
Sun protection index‡				
High score (≥3.5)	−0.07	0.07	0.94	.34
Low score (<3.5)	ref			
Sunburn in 2004-2007				
Any burn	0.12	0.07	1.13	.07
No burn	ref			
Usual daily sun exposure§				
Most-all the time	0.09	0.07	1.10	.16
Half time or less	ref			
Waterside vacation sun exposure//				
(No. waterside vacations birth-8 y)	0.03	0.01	1.03	.01
Interaction term				
Light hair × skin type II	−0.23	0.11	0.79	.03

Three-way interaction term of light hair × light skin color × type II was tested and was not significant.
Two-way interaction terms light hair × light skin and type II × light skin were tested and were not significant.
*Factor by which nevus counts change for every one-unit increase in predictor.
†Measures skin reflectance, higher values indicate lighter skin color.
‡Mean sun protection index from 2004-2007.
§Mean sun exposure from 2004-2007.
//Used as continuous variable in multiple regression.

contrary to the body of literature indicating that those with dark hair color have fewer nevi.[16,24,36-38] These relationships were independent of eye color, presence of freckling, sex, usual daily sun exposure, sunburn in 2004 to 2007, sun protection index, and waterside vacation sun exposure.

Previous studies that investigated phenotype and its relationship to nevus development have reported on the phenotypic main effects. Two studies that reported interactions between phenotype and nevus development did not approach the interaction term analysis systematically. Oliveria et al[18] observed a small subpopulation within their cohort with light skin, light hair, and a tendency to burn who had few nevi. However, the finding was reported only in the discussion of the article and did not distinguish among the Fitzpatrick skin types. Although Bauer et al[39] investigated all possible 2-way interactions, higher-order interaction terms were not evaluated nor were the 2-way interaction terms tested systematically. The significant interaction they reported was that children who are a Fitzpatrick type II with fair hair had greater numbers of incident melanocytic nevi than all other skin types. The differences between our findings and those of Bauer et al[39] are likely a result of differences in the study populations and definition of the dependent variable. Our study investigated the relationship between phenotype and nevus counts in 9-year-old children in Colorado whereas they examined German children from ages 2 to 7 years during a 3-year period, looking at incident nevi over that time period. Differences in altitude and climate between Germany and Colorado are likely to result in very different patterns of sun exposure, which may lead to differences in nevus acquisition. Further, there may be genetic differences between the two study populations.

It is widely accepted that those with red hair have fewer nevi compared with those with other hair colors.[15,27,28] Recent findings regarding *MC1R* polymorphisms suggest that the penetrance of the *MC1R* variants is additive, signifying that the more *MC1R* polymorphisms one has the lighter one's skin color, independent of hair color.[28] It is biologically plausible that non-red-haired individuals with *MC1R* variant genotypes may acquire fewer nevi similar to individuals with red hair. Therefore, it is possible that the lower nevus counts in our light-haired sun sensitivity type II children may be a result of *MC1R* variants.

It is also possible that children with light hair and sun sensitivity type II undergo nevogenesis at different rates than children with dark hair and sun sensitivity type II. Thus, children with light hair and sun sensitivity type II may eventually acquire similar numbers of nevi to their dark-haired counterparts, but may do so over a longer time span. The lack of relationship between the usual daily sun exposure and sun protection index variables and nevus counts could reflect an inability of parents to accurately report sun exposure, or the lack of precision in the

measures. It could also mean that genetic factors are more important than sun exposure in influencing nevus development. This is supported by two studies that found that genes account for about 67% of variation in nevus counts whereas environment accounts for 33%.[40,41] It could also mean that it takes very little sun exposure to induce nevus development in those who are genetically susceptible.

Our analysis of the relationship among hair color, sun sensitivity, and nevi by body location revealed that the finding of higher nevus counts among children with dark hair and sun sensitivity type II was present for nevi in intermittently sun-exposed body sites, but not for nevi in chronically exposed body sites. The "divergent pathway" model presented by Whiteman et al[42] may help to explain these findings. According to this model, in individuals who have a high propensity to develop nevi, melanocytes are initiated by sun exposure early in life and induced to proliferate and become neoplastic with little additional requirement for ultraviolet exposure. In individuals with a low propensity to develop nevi, chronic sun exposure is thought to be required for melanoma development. It is expected that in the first pathway, more melanomas will occur in intermittently exposed body sites (eg, the trunk), whereas in the second pathway, more melanomas will occur in chronically exposed body sites (eg, the head and neck). Research has generally supported the existence of these two pathways.[42-45] The children in our study with dark hair and sun sensitivity type II are most likely following the first pathway: they have a propensity to develop nevi on the intermittently exposed body sites with little sun exposure and would be expected to develop melanomas earlier in life and on intermittently exposed sites such as the trunk. Our blonde children with sun sensitivity type II have few moles and are therefore likely in the group that will develop melanoma through chronic sun exposure; their melanomas would be predicted to occur on the chronically exposed head and neck rather than the trunk, and later in life. This has clear implications for prevention. For the dark-haired children with many nevi, once initiation of melanocytes has occurred early in life it may be difficult to prevent the development of melanoma and early detection may need to be especially vigilant. For light-haired children with sensitive skin types but few nevi, primary prevention (avoidance of ultraviolet light) should be practiced throughout life, because we would expect them to develop melanoma through a pattern of chronic exposure. The lower nevus counts in these individuals may reflect presence of the nevus suppressing *MC1R* gene. Like redheads, who develop fewer nevi and have a high risk for melanoma, nevi may not be a good marker for melanoma risk among light-haired individuals with type II sun sensitivity. Studies that examine both nevus development and genetic factors should focus on this group to investigate whether *MC1R* polymorphisms, or other genetic factors such as those in a recent report,[46] could be contributing to the suppression of nevus development. Our team is in the process of collecting DNA specimens and testing this hypothesis.

Our findings emphasize that it is important to understand the heterogeneity of the relationship between phenotype and nevus development. The relationship we found should be examined in other studies of nevi in children, and in case-control studies of melanoma, to determine whether similar phenotypic interactions predict melanoma risk. This would provide the opportunity to discover how phenotype and nevus development in childhood relate to melanoma risk as an adult. In this regard, based on our findings in non-Hispanic white children, we predict that individuals with both dark hair and skin type II are among those with the highest risk for melanoma. Risk of melanoma in this group may have been previously underappreciated. Developing a clearer understanding of how differences in phenotype relate to nevus development and melanoma could lead to individualized primary and secondary prevention recommendations that may reduce melanoma incidence and mortality.

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