Published in final edited form as:

J Invest Dermatol. 2014 September ; 134(9): 2469–2471. doi:10.1038/jid.2014.189.

FACTORS ASSOCIATED WITH NEVUS VOLATILITY IN EARLY ADOLESCENCE

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TO THE EDITOR

We previously reported that volatility – appearance and disappearance – of nevi is common during adolescence. With high-resolution imaging that allows detection of changes in individual nevi, we observed that 75% of children followed between ages 11 and 14 had at least one new back nevus and 28% had at least one back nevus which disappeared (Scope *et al*., 2011). As nevi are intermediate markers of melanoma risk, an improved understanding of their biology has implications for melanoma prevention. Herein, we aimed to identify the risk factors associated with nevus volatility between ages 11 and 14.

Study of Nevi in Children (SONIC) (Oliveria *et al*., 2009; Geller *et al*., 2007; Scope *et al*., 2008) was approved by Institutional Review Boards at Boston and Harvard Universities. The cohort of 365 children included 140 females (38.4%). Distribution by ethnicity was

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CONFLICT OF INTEREST

The authors state no conflict of interest.

white – 268 (73.4%), Hispanic – 65 (17.8%), and other (African-American, Native-American, Asian) – 32 (8.8%).

We surveyed students and collected data on demographics, phenotype (skin, eye and hair color), sun-sensitivity, sun-exposure and -protection practices, and frequency of sunburns at ages 11 (5^{th}-grade baseline) and 14 (8^{th}-grade follow-up). Overview back photography and dermoscopic imaging of up to 4 index back nevi were performed at baseline and follow-up; dermoscopic imaging of up to two new back nevi was also obtained at follow-up. Methodology for image analysis was previously described and the same methodologies were utilized at baseline and follow-up (Scope *et al*., 2011). For each student, we created a categorical variable based on dermoscopic pattern of their index nevi: (1) reticular-globular: ≥1 globular nevus and ≥1 reticular nevus were observed, (2) reticular: ≥1 reticular nevus and no globular nevi, (3) globular: ≥1 globular nevus and no reticular nevi and, (4) no pattern: homogenous nevi, without reticular or globular nevi.

We created composite variables for longitudinal measures of sunburn, outdoor cumulative sunexposure, and sun-protection using baseline and follow-up surveys (Online Supplementary Figures 1-3). We performed linear regression, univariate and multivariate regression analysis of risk factors for continuous outcomes: appearing nevi and total back nevus counts at age 14, using the following variables: baseline nevus count, sunburn, dermoscopic pattern and gender. We also adjusted for ethnicity, sun sensitivity index (Scope *et al*., 2011), cumulative sun-exposure, sun-protection and freckling. Logistic regression was employed for the binary outcome of disappearing nevi. The rate ratios for linear regression and odds ratios for logistic regression were derived by exponentiating estimated parameters. Corresponding 95% confidence intervals (CI) and p-values are also reported. We further explored effect of baseline nevus count by conducting stratified multivariate modeling. Analyses were carried out using SAS/STAT®.

Characteristics of participants at baseline and follow-up are shown in Online Supplemental Table 1. Mean back nevus count increased from 8.2 (SD 8.8) to 11.3 (SD 11.8). Percentage of students with at least 15 back nevi (highest category) increased from 13.1% at baseline to 22.7% at follow-up.

Baseline nevus counts were strongly associated with higher nevus counts at age 14 (Table 1). Children were likely to be categorized to the same nevus count quartile at baseline and follow-up (McNemar's test for concordance $p<0.01$); nearly 95% of children assigned to highest back nevus count quartile at age 11 were still classified to highest quartile at age 14.

Baseline nevus counts were also strongly associated with appearance of new nevi and disappearance of existing nevi (Table 1 and Figure 1). The likelihood of stability, i.e. having the same nevus counts at baseline and follow-up, decreased as baseline nevus counts increased (Figure 1). While disappearance of a nevus was observed in students across the range of baseline nevus counts, disappearance of ≥2 nevi was more frequent in participants with higher baseline nevus counts (Figure 1). Of 5 participants with ≥3 disappearing nevi (range 3-11), 4 were in the highest quartile of baseline nevus counts. In addition, globular

dermoscopic pattern was significantly associated with appearance of new nevi and higher back nevus counts at age 14 (Table 1).

Because baseline nevus count was strongly associated with the outcomes of interest, we conducted stratified analyses by quartiles of baseline nevus counts, to better understand the role of other risk factors. We observed a significant association between sunburn and higher nevus counts at age 14, only in the group of children with the highest quartile of back nevus counts at age 11 (adjusted rate ratio 1.40 [95% CI 1.02-1.92] for having ≥1 sunburns, compared to no sunburn).

Nevus phenotype, while predominantly genetically-driven (Bataille *et al*., 2000; Bataille *et al*., 2007; Milne *et al*., 2008; English DR *et al*., 1994; Siskind *et al*., 2002), manifests gradually during the first decades of life. We found that by age 11, the predisposition for displaying a high nevus count later in adolescence has been largely established. Our imaging methods demonstrated that the increase in nevus counts between ages 11-14 results from appearance of new nevi exceeding disappearing of existing nevi. Children with highest nevus counts demonstrated the greatest nevus volatility, frequently displaying concurrent appearance and disappearance of nevi.

While nevus volatility increases with increasing nevus counts, the relationship does not appear to be directly stochastic. This suggests external or intrinsic factors may be at play. We studied sun- exposure effects by surveying outdoor exposure, sun-protection behaviors, and sunburn. Among these variables, only sunburn showed a statistically significant association with total back nevus count. This may reflect a biological impact of sunburning itself, or lack of power to detect an effect of other measures of sun exposure and protection.

Finally, our analysis suggests nevus volatility may differ between subsets of nevi classified by their dermoscopic pattern. We found that only globular pattern was associated with appearance of new nevi. While our observation is predicated on a small number of index nevi imaged dermoscopically and a classification based on overall dermoscopic pattern, the findings are in line with recent studies suggesting dermoscopic classification may distinguish between biologic subsets of nevi (Scope *et al*., 2008; Scope *et al*., 2011; Zalaudek *et al*., 2006; Argenziano *et al*., 2007; Changchien *et al*., 2007; Seidenari *et al*., 2006; Zalaudek *et al*., 2011).

In summary, we have found that nevi demonstrate considerable volatility in adolescence which is greatest among the children with the highest baseline nevus counts. While preliminary, our data implicate sunburn and dermoscopically recognized subsets of nevi as factors contributing to nevus volatility in adolescence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the teachers and staff in the Framingham School System and the parents and students who participated in this study. This research was supported by a grant provided by the National Institutes of Health (funding source number R01AR049342).

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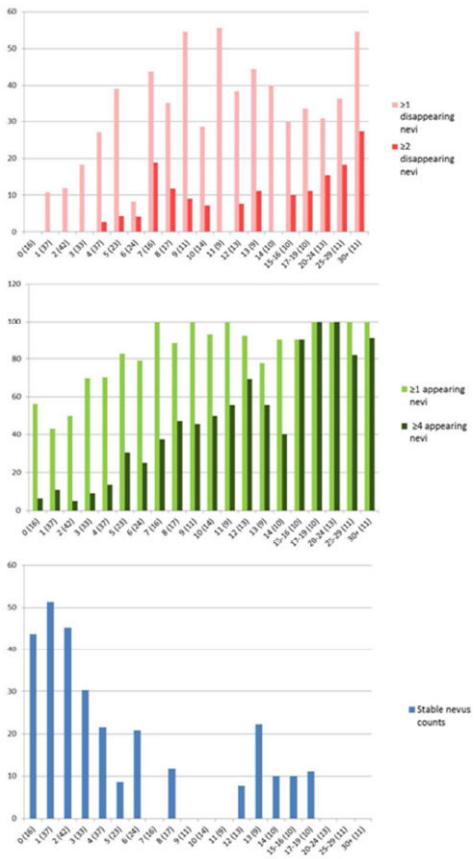

Figure 1.

Frequency of students with disappearing nevi, appearing nevi and stable nevus count by baseline nevus count.

(X-axis - baseline nevus count (number of children); Y-axis – percentage)

Table 1

Risk factors of nevus volatility, total back nevus counts at age 14, appearance of new nevi, and disappearance of existing nevi adjusted for ethnicity, sun-sensitivity index, cumulative sun-exposure, sun-protection and freckling.

		Total back nevus counts at age 14	**Appearance of new nevi**	**Disappearance of existing nevi**
Variable	N	Adjusted Rate Ratio (95% CI)*	Adjusted Rate Ratio (95% CI)*	Adjusted Rate Ratio (95% CI)*
Sunburn‡				
None	104	1.00 (referent)	1.00 (referent)	1.00 (referent)
At least one sunburn	261	1.09 (0.98 -1.20)	1.20 (0.98-1.47)	0.74 (0.51-1.09)
Baseline nevuscount at age 11‡‡				
0-2 nevi	95	1.00 (referent)	1.00 (referent)	1.00 (referent)
3-5 nevi	93	1.85 (1.64 -2.09)	1.25 (0.97-1.60)	1.44 (0.74-2.18)
6-11 nevi	91	3.35 (2.94 -3.82)	1.98 (1.52-2.57)	1.92 (1.16-3.16)
≥12 nevi	86	7.25 (6.31 -8.32)	3.41 (2.57-4.51)	2.58 (1.17-4.53)
Gender				
Female	140	1.00 (referent)	1.00 (referent)	1.00 (referent)
Male	225	1.08 (0.99 -1.17)	1.13 (0.96-1.34)	0.98(0.21-1.75)
Dermoscopic Pattern				
Homogenous	107	1.00 (referent)	1.00(referent)	1.00(referent)
Globular	96	1.12(1.01 – 1.24)	1.27 (1.04-1.55)	0.97(0.61-1.53)
Reticular	91	0.95(0.84 – 1.08)	1.04 (0.81-1.33)	1.31 (0.73-2.36)
Reticular & Globular	51	0.98(0.86 – 1.11)	0.97 (0.75-1.24)	1.27(0.73-2.21)

*CI = Confidence interval

‡Quantification of how many times in the past summer students were sunburned; As composite variable of sunburning, participants were categorized into 2 groups: participants reporting no sunburns at both time points; 1 or more sunburns at either or both time points

‡Categories based on quartiles of nevus counts at baseline