

Is High Mole Count a Marker of More Than Melanoma Risk?

Eczema Diagnosis Is Associated With Melanocytic Nevus in Children

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Background: The number of melanocytic nevi is the best single marker of increased melanoma risk. In a previous study, adults with severe eczema were reported to have significantly fewer nevi than adults without eczema.

Observations: In a nested case-control design within a randomized, controlled interventional trial of additional sun protection vs standard care in 269 children, a history of eczema was reported by the parents of 44 (16%) of the children. More nevi were found in children with a parental report of previous eczema diagnosis than in children without reported eczema (median, 7.5 nevi vs 5.0 nevi; $P = .01$). Eczema diagnosis was most significantly associated with more melanocytic nevi in children with

lightly pigmented skin (8.5 nevi vs 6.0 nevi; $P < .001$). In multivariate logistical regression analysis, including assessment of hair color, sun protection practices, and study assignment (intervention vs standard care), eczema status remained significantly predictive of nevi number in children ($P < .001$).

Conclusions: In contrast to a previous study that associated severe eczema with fewer nevi in adults, in the present study children with a reported history of eczema had more nevi than children without a reported history of eczema.

Arch Dermatol. 2004;140:577-580

AN INCREASED NUMBER OF acquired melanocytic nevi is one of the strongest phenotypic risk factors for melanoma.^{1,2} Factors associated with increased number of nevi include sun exposure,^{2,3} poor sun tolerance,⁴ skin and hair pigmentation,^{2,5} and immunosuppression.^{6,7} Loss of nevi has been associated with increased age.⁸

Interestingly, adults with severe eczema, an inflammatory skin disease, have recently been reported to have significantly fewer nevi than matched controls.⁹ These findings suggest that adults with eczema might express factors or be exposed to therapy that inhibits the growth of melanocytic cells. Although eczema occurs in only 1% to 3% of adults,¹⁰ it affects more than 10% of children.¹¹ In the present study, we examined the relationship between eczema and nevi in children to determine whether a decreased number of nevi are also found in children with eczema.

METHODS

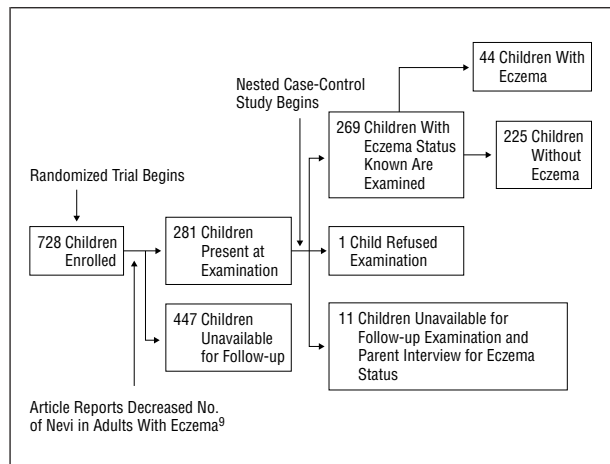
This study used a nested case-control design within a randomized, controlled interventional trial of additional sun protection vs standard care for a cohort of children (**Figure**). Par-

ents enrolled at 14 Colorado Kaiser Permanente Health Maintenance Organization primary care practices with children born between March and October 1998 were identified using hospital birth records and recruited by telephone within 6 months after childbirth. Recruitment included an initial screening for skin cancer risk, and parents of children with brown or black skin, brown eyes, and dark-brown or black hair were informed that the study might provide less benefit owing to their child's lower lifetime risk for skin cancer.

Practices were matched by patient volume, number and type of providers, and population sociodemographic profiles and randomized to intervention (additional sun protection advice and materials) or standard care. Intervention groups received additional sun protection advice from health care providers during routinely scheduled pediatric visits and sun protection materials (eg, hats, sunglasses, and sunscreen samples). The control group received standard care. This study was approved by the Colorado Multiple Institutional Review Board in 1997. In 2001, the Colorado Multiple Institutional Review Board approved an amendment allowing the examination of eczema status as a secondary end point of the study.

Skin examinations and parent interviews were conducted when the children were approximately 3 years of age (June 1-August 31, 2001). Examinations included assessment of

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Flow diagram of study design. Eczema status defined by parental report (see "Methods" section).

eye color (visual assessment), hair color (wigmaker sample matching), and degree of freckling. Nevus counts were performed by 1 of 3 dermatologists or 1 specially trained pediatrician with procedures used in previous studies of nevi in children.^{12,13} Interrater reliability of all 4 examiners was measured by blinded examination of a sample of 45 children. Skin color was determined using colorimeter (Minolta Chromameter 300) measurements of the ventral surface of the arm (untanned region) and paint-chip sample matching. Three pigmentation groups were defined by colorimeter readings (ie, light, ≤ 13.9 ; medium, > 13.9 to ≤ 16.0 ; and dark, > 16.0).

To assess eczema diagnosis status, parents were asked, "Has a healthcare professional ever told you that your child has eczema or atopic dermatitis? (yes/no)." If yes, the parent was asked to estimate how long the child had eczema or atopic dermatitis (number of months). Skin cancer knowledge, child sun exposure history, and sun protection habits were also assessed. Parents were asked whether they "always (4 points), frequently (3 points), seldom (2 points), or never (1 point)" used the following 7 sun protection strategies when their child was outside for more than 15 minutes between 11:00 AM and 3:00 PM: would they have the child (1) stay inside during midday, (2) stay in the shade, (3) use clothing that covers most of the arms and legs, (4) use sunscreen with a sun protection factor greater than or equal to 15, (5) use a hat, (6) use sunglasses, and would they (7) limit the child's time in the sun? Responses regarding use of the 7 strategies were combined to create the Sun Protection Scale, with a score ranging 7 (no strategies used ever) to 28 (all strategies used always).

Statistical analyses were performed using SPSS software (SPSS Inc, Chicago, Ill). Comparisons of baseline characteristics of children with and without eczema were performed using the χ^2 test for categorical variables and the t test for continuous variables. The Pearson correlation coefficient was used to assess interrater reliability for nevus counts. The Mann-Whitney U test was used for nonparametric testing of median nevus counts in children with and without eczema, and logistical regression analysis was performed for a priori covariates and eczema status.

RESULTS

Two hundred eighty-one (39%) of 728 children initially enrolled were examined after 3 years (Figure). The reason that the vast majority of the children were unavailable for examination was because their parents could not be reached.

Table 1. Characteristics of 3-Year-Old Children*

	Children With Eczema (n = 44)	Children Without Eczema (n = 226)	P Value
Sex			
M	57	47	.25
F	43	53	
Race			
White	77	85	.37
Black	2	1	
Asian	7	2	
Hispanic	14	11	
Skin color†			
Light	55	56	.17
Medium	20	29	
Dark	25	15	
Freckling			
Any	9	17	.20
None	91	83	
Hair color			
Blond/red	23	30	.31
Light-brown	35	40	
Brown/black	42	30	
Eye color			
Brown	39	32	.39
Blue/green/hazel	61	68	
Sun Protection Scale mean score‡	18.3	18.1	.72
Intervention group status			
Intervention	48	50	.78
Control	52	50	

*All values other than P values and Sun Protection Scale mean scores are expressed as percentages. Baseline characteristics for all 281 children who were examined are not reported, as eczema status was obtained for only 270 children. One child refused examination; therefore, eczema status and skin examination data were available for 269 children. All children were born between March and October 1998.

†See "Methods" section for colorimetric measurements defining skin color groups.

‡See "Methods" section for components of Sun Protection Scale.

Additional efforts to obtain parental contact information included searching Department of Motor Vehicle records and attempting to contact the parent designated *significant other*. The refusal rate comprised fewer than 5% of the enrollees. Answers to questions regarding eczema diagnosis history were obtained for 269 (96%) of the 281 children who were present at examination. Comparison of the children who were present at examination ($n = 281$) with those who were not ($n = 447$) revealed that the parents of examined children were more likely (1) white, non-Hispanic race ($P \leq .03$), older ($P \leq .001$), more educated ($P \leq .001$), and higher salaried ($P = .005$); (2) to report a family member (child, sibling, or parent) with a skin cancer (31% vs 23%; $P = .02$); and (3) to agree with the statement that a child who gets sunburns is more likely to develop skin cancer as an adult (90% vs 83%; $P = .08$).

Baseline characteristics, Sun Protection Scale, and intervention group status did not differ between examined children with and without a history of eczema diagnosis (Table 1). The prevalence of eczema diagnosis was 16%. Good interrater reliability for nevus counts was observed (Pearson correlation coefficient, 0.80).

Children with a history of eczema diagnosis had more nevi (median, 7.5 nevi) than children without (median,

5.0 nevi; $P=.01$) (**Table 2**). Duration of eczema, for more or less than 2 years, was not associated with nevi number (7.5 and 7.6 nevi, respectively).

Children in the 3 pigmentation categories (light, medium, and dark) did not differ significantly with regard to prevalence of eczema diagnosis (Table 2). Eczema diagnosis was associated most strongly with an increased number of nevi in children with lightly pigmented skin (8.5 nevi vs 6.0 nevi; $P<.001$).

Logistical regression analysis was performed using a priori covariates: hair color, sun protection practices, and study assignment (intervention vs control). Among the children with light pigmentation, the diagnosis of eczema remained a strong predictor of nevi ($\beta=3.3$; $P<.001$). Overall, this model accounted for 20% of the variance of nevi, and the diagnosis of eczema accounted for half of the variance explained (10%).

COMMENT

Using the single question with the best predictive accuracy (92%) of eczema status, we found an eczema prevalence (16%) similar to previously reported rates.¹¹ In contrast to eczema in adults,⁹ eczema in children was associated with increased number of nevi (7.5 nevi vs 5.0 nevi; $P=.01$). The number of nevi in adults with eczema from a previous study⁹ and children with eczema from the present study may have differed for several reasons: (1) adults may have had more severe eczema; (2) adults may have had years of eczema therapies to which children may never have been exposed; (3) nevi smaller than 2 mm were included in the nevus counts in children but not in adults; (4) eczema may have caused an alteration in the nevus life cycle, increasing the number of nevi transiently during early childhood; or (5) chronic persistent eczema may have led to the elimination of nevi in adults.

The life cycle of nevi has been described with the number of nevi peaking in the second or third decade of life and decreasing later, with disappearance by the seventh to ninth decade.^{8,14} Sun exposure may hasten the maturation and subsequent elimination of nevi.¹⁴ Just as sun exposure has been theorized to speed the maturation of nevi, eczema might also alter the nevus life cycle. For example, extensive, prolonged skin inflammation due to eczema might lead to increased rejection and elimination of nevi by the immune system.

The skin inflammation characteristic of eczema causes the release of cytokines (interleukins 4, 5, 9, and 13) and the production of arachidonic acid metabolites.¹⁵ Also, basophils from patients with eczema release leukotriene C4 when they are exposed to enterotoxins from *Staphylococcus aureus*, a frequent bacterial colonizer of patients with eczema.¹⁶ Leukotriene C4 is a potent mitogen for melanocytes^{17,18} that may mediate increased melanocytic proliferation in children with eczema.

The number of nevi was highest in lightly pigmented children with eczema. The influence of skin pigmentation and eczema on nevus number needs further investigation, but these results suggest that melanocytes from lightly pigmented skin may be more sensi-

Table 2. Nevus Counts in Pigmentation Groups, With and Without Eczema

	No. of Children With Eczema (No. of Nevi, Median [SD])	No. of Children Without Eczema (No. of Nevi, Median [SD])
All patients	44 (7.5 [4.7])*	225 (5.0 [3.8])*
Children with		
Light pigmentation	24 (8.5 [4.1])†	124 (6.0 [3.5])†
Medium pigmentation	9 (5.0 [6.1])	67 (5.0 [4.4])
Dark pigmentation	11 (4.0 [3.5])	34 (4.0 [3.0])

* $P=.01$.

† $P<.001$.

tive to cytokine stimulation. Such differences have been noted in vitro: melanocytes isolated from lightly pigmented skin grow more easily than those from darkly pigmented skin (Joseph J. Yohn, MD, oral communication, June 1, 1991).

Although the present study represents the largest US cohort of children followed up from birth for the development of melanocytic nevi, it has limitations:

1. Complete follow-up information was obtained on 37% of the initial participants and raises the specter of selection bias. Nonetheless, selection bias is unlikely to explain such a striking finding in the absence of a priori reasons for the preferential participation of either (1) children without eczema and fewer nevi or (2) children with eczema and more nevi.
2. Eczema status was determined by parent report that might have been subject to misclassification. Extensive misclassification, however, is unlikely given that this measurement tool has been reported to be 92% accurate.¹¹
3. Another possible misclassification includes incorrect identification of nevi as nonnevus skin lesions or vice versa. Such misclassification was again unlikely, as physicians performing skin examinations used validated classification systems^{12,13} and good interrater reliability was observed.
4. Given that this study sampled subjects with greater sun sensitivity, the results of this study may not be applicable to other populations.
5. Finally, eczema treatment was assumed to be limited to topical therapy in the children but was not directly assessed.

Given these limitations, the relationship between eczema and nevi merits further exploration.

Previous studies indicate that an increased number of nevi reflects both solar exposure and increased risk for melanoma. If eczema affects nevus count, the risk of melanoma in patients with eczema merits further examination. The degree to which increased nevus number in children with eczema reflects sun exposure, increased melanoma risk, or a history of cutaneous inflammation remains to be determined.

Accepted for publication October 22, 2003.

This study was supported in part by grants K-07 CA92550-01A1 (Dr Dellavalle) and R01-CA 74592 (Drs

Crane and Morelli) from the National Cancer Institute, by grant T32 AR07411 from the National Institutes of Health (Dr Hester), and by research grants from NCI Cancer Education Grant R25 CA49981, Bethesda, Md.

We thank Patrick Diaz, Kristie McNealy, Patricia Cisneros, Joshua Visitacion, Azita Jacobson, Tuyet-Hong Pham, Rickia Furness, Nikki Singh, and Lisa Bolan for helping conduct the study; William Weston, MD, Lisa Schilling, MD, and David Norris, MD, for stimulating discussion; and Amanda Drake for technical assistance.

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