Broad-Spectrum Sunscreen Use and the Development of New Nevi in White Children

A Randomized Controlled Trial

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Context High nevus density is a risk factor for cutaneous malignant melanoma. Melanocytic nevi originate in childhood and are largely caused by solar exposure.

Objective To determine whether use of broad-spectrum, high–sun protection factor (SPF) sunscreen attenuates development of nevi in white children.

Design Randomized trial conducted June 1993 to May 1996.

Setting and Participants A total of 458 Vancouver, British Columbia, schoolchildren in grades 1 and 4 were randomized in 1993. After exclusion of nonwhite children and those lost to follow-up or with missing data, 309 children remained for analysis. Each child's nevi were enumerated at the start and end of the study in 1996.

Intervention Parents of children randomly assigned to the treatment group (n=222) received a supply of SPF 30 broad-spectrum sunscreen with directions to apply it to exposed sites when the child was expected to be in the sun for 30 minutes or more. Children randomly assigned to the control group (n=236) received no sunscreen and were given no advice about sunscreen use.

Main Outcome Measure Number of new nevi acquired during the 3 years of the study, compared between treatment and control groups.

Results Children in the sunscreen group developed fewer nevi than did children in the control group (median counts, 24 vs 28; $P=.048$). A significant interaction was detected between freckling and study group, indicating that sunscreen use was much more important for children with freckles than for children without. Modeling of the data suggests that freckled children assigned to a broad-spectrum sunscreen intervention would develop 30% to 40% fewer new nevi than freckled children assigned to the control group.

Conclusions Our data indicate that broad-spectrum sunscreens may attenuate the number of nevi in white children, especially if they have freckles.

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A STRONG RISK FACTOR FOR THE development of cutaneous malignant melanoma (CMM) in white populations is the presence of acquired melanocytic nevi.[1-4] There is a consistent rise in risk of CMM with increasing number of nevi in virtually every study that has assessed this relationship.[3-6] The presence of remnants of preexisting nevi in about 50% of CMMs[7] indicates that acquired nevi are precursor lesions for many,[8,9] although not all, melanomas.[9]

Recent work has focused on the origin and etiology of nevi in children, who are, for the most part, born without nevi. Fewer than 2% of children have a congenital nevus,[10,11] although acquired nevi begin to become clinically obvious at an early age.[12] Etiologic studies have shown that host and pigmentary characteristics (eg, light skin color, freckling, propensity to burn in the sun) that raise adult risk of CMM also predispose children to develop high nevus density.[13-16] Genetic factors also influence nevus prevalence, with higher counts of melanocytic nevi in melanoma-prone families.[17,18] The principal environmental risk factor for the development of acquired nevi is sunlight exposure as measured by sunburn history,[13] latitude of residence,[19] or reported solar exposure.[14,16]

Reducing acquired nevi in children may reduce their risk of CMM as adults. With this in mind, we have conducted a randomized controlled trial to see whether broad-spectrum high–sun protection factor (SPF) sunscreen use might attenuate the number of new nevi that develop in white children.

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MATERIALS AND METHODS

Study Design and Data Collection

The study was approved by the British Columbia Cancer Agency and University of British Columbia research ethics committees. Six Vancouver elementary schools with the largest proportion of white children were selected for the study. School principals were approached for permission to conduct the study within their schools. After securing permission from the Vancouver School Board, the principals released names of all children in grades 1 and 4 (aged 6-7 and 9-10 years, respectively) and their parents to the study. Parents were sent a letter explaining the study and were asked for written permission to examine each child and enroll the child and a parent in the 3-year investigation.

At enrollment, each student was examined by either a dermatologist (J.K.R.) known for his expertise in childhood nevus studies[19-21] or by a physician specially trained by him. All nevi, regardless of size, were counted using techniques outlined in the International Agency for Research on Cancer counting protocol.[21] The scalp, genital area, and buttocks were not examined, nor was the breast area in girls.

Degree of freckling on the face, shoulders, and arms was estimated using a chart[13] with good observer reproducibility. Height and weight of each child were taken to allow calculation of body surface area.[22] Skin reflectance on a non–sun-exposed site (upper inner arm) was measured using a reflectance spectrophotometer set to 680 nm. Parents of each child completed a detailed questionnaire, assessing the child's ethnic origin, sun sensitivity, sunburn history, and holiday sunlight exposure to the time of randomization.

Children were individually randomized by the study statistician (A.J.C.) to the sunscreen (intervention) or the ambient use (control) group. The statistician had no contact with the physicians counting nevi or with the study subjects. Parents of those randomized to the sunscreen group received a bottle of SPF 30 broad-spectrum sunscreen near the end of each school year in June 1993, 1994, and 1995. Parents were instructed to apply the sunscreen in amounts they usually used to all sun-exposed sites on the enrolled child whenever he/she was expected to be in the sun for 30 minutes or more. Parents were specifically asked to use the particular bottle of sunscreen only on the enrolled child. At the end of July each year, a second bottle of sunscreen was sent. Parents were then asked to measure and report how much of the original bottle had been used by marking what remained in the first bottle on an actual-size diagram of the sunscreen bottle. Parents were instructed to use the second bottle of sunscreen on the index child for the remainder of the summer and the next Christmas and spring breaks. Parents whose children were randomized to the control group were given no advice as to sunscreen use, and no placebo was provided. Because of the level of general education about sun exposure, however, use of sunscreen was substantial in the control group.

At the end of each summer vacation, solar exposure during the previous 3 months was determined for children in each study group using an activity-based questionnaire. Clothing preference and sunscreen use during outdoor activities were assessed on a semiquantitative basis. Similar instruments were used to evaluate solar exposure during the Christmas and spring breaks each year. As Vancouver is a relatively low-sunlight area and records high temperatures only in the summer, evaluating summer exposure plus the other 2 school holiday periods each year captures most solar exposure in children.

In May 1996, all children retained in the study were reexamined by physicians, and their nevi were enumerated once again. Physician-counters did not know to which study group children had been assigned. To ensure that nevus counts were concordant among counters, 69 (15%) of the students were counted by 2 of the 3 physicians and 17 (4%) were counted by all 3 physicians. Assuming the variance among the duplicate and triplicate counts was typical, the proportion of variance in whole-body nevus counts attributable to the effect of the counter was less than 5%.

Data were used only if students completed the whole protocol, defined as the intake and exit nevus counts, the intake questionnaire, and at least 2 of the 3 summer sun update, Christmas break, and spring break questionnaires. If 1 of the summer sun updates was not completed, mean values from the other 2 such questionnaires were substituted. The same procedure was followed for missing Christmas and spring break questionnaires.

Data Analysis

It is customary in clinical trials to conduct an analysis based on intent-to-treat. In this study, no intermediate nevus counts were taken between randomization and conclusion. It is therefore not possible to conduct an intent-to-treat analysis based on imputed end-point values for subjects who were lost to follow-up during the course of the study.

Several measures of sun exposure were calculated. Minimal erythemal dose (MED) information for clear sky conditions by latitude and month of the year were obtained from Diffey and Elwood.[23] Vacation solar exposure in MEDs during the 3 years was assessed using location, latitude, and month of the vacation, assuming that vacation exposure took place during peak, daylight UV-B exposure hours. Total UV exposure from vacation and recreational activities in MEDs, adjusted for clothing worn while outdoors, was also calculated by anatomic subsite. Because it was not possible to directly measure whole-body exposure, MED values for each of the 4 anatomic subsites were simply summed in each subject to get the whole-body score.

Whole-body nevus counts from 1993 were subtracted from 1996 counts for each child, giving the number of new nevi. All nevi regardless of size were included in the counts. Comparisons between study groups were based on medians, and differences were assessed using the Kruskal-Wallis test.

A linear regression model to account for the number of new nevi was fitted, using the following predictor variables: treatment group, school grade (equivalent to age), sex, skin reflectance value, facial freckling, hair color, skin reaction to sunlight, family history of skin cancer, sunburn history to age 5 years, sunburn history during 1993 through 1996, hours spent outdoors during 1993 through 1996, vacation sun exposure during 1993 through 1996, and total sun exposure during 1993 through 1996 adjusted for clothing. The variables sex, grade, skin reaction to sunlight, treatment group, and hair color (dark brown, light brown, blond, red) were modeled as categorical variables and all others as continuous variables.

The baseline model included sex, grade, hair color, and treatment group. Additional variables were added to the baseline model using a forward-selection algorithm, with inclusion restricted to factors with a significance level of $P<.10$. An inspection of plotted data suggested potential interactions between treatment group and other predictor variables. Consequently, in the initial stages of multivariate analysis, variables were added to the model as a combined main effect and interaction-with-treatment-group effect. Significance of these variables was assessed according to the *P* value of the interaction effect rather than the main effect.

After including variables with significant interaction effects, subsequent modeling was performed to test for the significance of the remaining independent variables. Residual plots were used to confirm the independence, normal distribution, and constant variance of the errors.

RESULTS

A total of 696 children (354 in grade 1 and 342 in grade 4) were ascertained in the 6 schools. Of these, 458 (66%) were enrolled in the study and randomized to either the sunscreen or control group. At the completion of the trial 3 years later, 393 (86%) remained. The children in the study were largely white (323 [82%]); Chinese Canadian and other Asian Canadian students (37 [9%]) made up the second-largest ethnic group. The number of Asian Canadian and dark-skinned subjects was small, and, as they acquire few new nevi with age[20] and are at low risk of eventual cutaneous melanoma,[24] they were eliminated from consideration prior to beginning the analysis. Six grade 1 and 8 grade 4 students with missing nevus-counter identification were excluded, leaving 309 white children for the final analysis (FIGURE 1).

The median nevus counts at intake were 41 for grade 1 students (aged 6-7 years) and 68 for grade 4 children (aged 9-10 years). The distribution of nevi at intake was skewed positively, with a few children having very high counts. No child had a count of zero.

Factors such as hair color, skin reaction to sunshine, facial freckling, and sunburn score in the first 5 years of life demonstrated associations with nevus counts similar to those seen in previous studies, as shown in TABLE 1. Skin reflectance value at 680 nm did not demonstrate a significant relationship with nevus frequency.

Analysis of the number of new nevi revealed that children in the sunscreen group developed significantly fewer new

Figure 1. Trial Profile

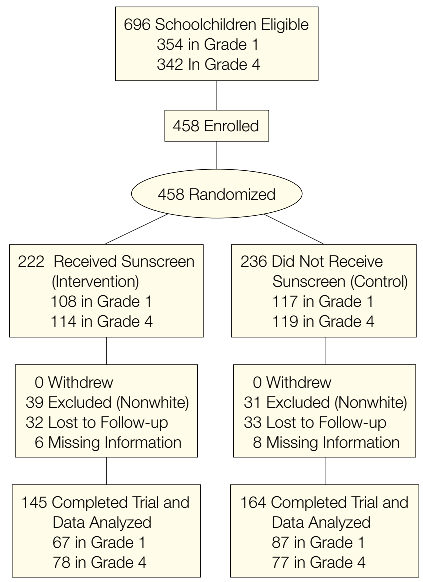


Table 1. Intake Nevus Count (1993), Pigmentation Characteristics, and Sunburn Score Among White Students

	No. of Subjects				
	Sunscreen Group	Control Group	Total	Median Nevus Count	P Value*
Skin reflectance					
Dark	48	56	104	55.5	.72
Medium	47	56	103	53.0	
Light	50	52	102	50.5	
Hair color					
Dark brown	46	58	104	59.0	<.001
Light brown	41	45	86	53.5	
Red	10	10	20	27.0	
Blond	48	51	99	51.0	
Freckles on face					
Few or none	52	62	114	42.0	<.001
Moderate	36	53	89	53.0	
Dense	57	49	106	66.5	
Sunburn score, first 5 years					
Grade 1					
Low	28	51	79	38.0	.07
High	39	36	75	43.0	
Grade 4					
Low	39	41	80	62.0	.02
High	39	36	75	78.0	

*Kruskal-Wallis test for difference in medians.

nevi than those in the control group (median counts, 24.0 vs 28.0; $P=.048$). A comparison using mean values showed an even greater difference (28.8 vs 34.6). A few children had a lower nevus count in 1996 than in 1993.

TABLE 2 compares measures of sunlight exposure in the 2 treatment groups. Time spent outdoors from 1993-1996 was very similar among the students in each study group. No difference in vacation solar exposure from 1993-1996 in MEDs was seen between the sunscreen and control groups, and no major difference was seen in total sunlight exposure adjusted for clothing coverage for whole-body or anatomic subsite (Table 2).

Use of sunscreen was assessed by anatomic subsite (TABLE 3). When sunscreen was used, exposure was defined as protected and when not used, as unprotected. Median number of episodes of protected and unprotected exposure during the observation period showed a greater proportion of unprotected episodes in the control group at each subsite. The majority of study subjects in both the sunscreen and control groups reported zero episodes of trunk exposure unprotected by sunscreen, creating artificially low medians. Mean values provide more credible estimates and show an excess of unprotected episodes in the control group compared with the sunscreen group (7.7 vs 5.2).

A model of the effects of the independent variables on the whole-body number of new nevi is presented in TABLE 4. Total sunlight exposure, adjusted for clothing, school grade (age), the interaction term for sunscreen group, and degree of facial freckling, appears to predict nevus counts. The interaction between being randomized to the broad-spectrum sunscreen group and degree of freckling is statistically the strongest predictor of new nevi. FIGURE 2 shows that the importance of being randomized to the sunscreen group increases with increasing degree of freckling. Removing subjects with the greatest number of new nevi had little effect on the divergence of the regression lines for subjects in the 2 study groups.

To further assess the difference in number of new nevi between subjects with and without facial freckles, models were constructed separately for grade 1 children and grade 4 children, with subjects dichotomized into 2 groups: those with ≤10% freckling (no freckles), and those with >10% freckling density (freckles). The model predicted that grade 1 children who had freckles would have about 40% fewer new nevi after 3 years when randomized to the sunscreen group rather than the control group. Grade 4 children with freckles randomized to the sunscreen group would have about 30% fewer new nevi than if they were randomized to the control group. Children with no freckling in grades 1 and 4 would have little advantage when randomized to the sunscreen group compared with the control group.

Finally, if sunscreen attenuates the development of new nevi, it might be expected that, after control for freckling, subjects in the intervention group who used the most sunscreen would have the fewest new nevi. FIGURE 3 (grade 4 children presented; grade 1 graph similar) also demonstrates that this is the case, and, although the differences are not statistically significant, there is an inverse relationship between sunscreen use and new nevi.

Table 2. Solar Exposure Variables by Randomization Group*

UV Variable	Sunscreen Group: No. of Subjects	Sunscreen Group: Median	Control Group: No. of Subjects	Control Group: Median
Time spent outdoors, 1993-1996, h	144	357.0	154	361.5
Vacation solar exposure, 1993-1996, MEDs†	131	962.5	140	962.5
Total sunlight‡ exposure adjusted for clothing coverage, 1993-1996, MEDs	131		142	
Face, neck, and ears		421.7		420.8
Trunk		148.2		149.0
Upper limbs		391.4		391.5
Lower limbs		275.0		276.0
Whole body		1252.2		1214.3

*Minimal erythemal dose (MED) information from the tables of Diffey and Elwood.[23]
†Calculated from number of weeks of holiday, latitude, and number of clear sky MEDs per day.
‡Based on reported outdoor activity each month, assumed to occur between noon and 1 PM. Clothing adjustment based on type of activity and clothing preference of each subject. Whole body index composed of values for the 4 anatomic sites summed for each subject.

COMMENT

To our knowledge, this is the first randomized trial of the use of sunscreen as a chemopreventive agent for attenuating nevi in children. Strengths of the study include individual rather than group randomization and blinding of the nevus counters to the status of the chil-

Table 3. Use of Sunscreen During Episodes of Summer Recreational Activity

Anatomic Site	Sunscreen Group: No. of Subjects	Sunscreen Group: Median No. of Protected Sun Episodes	Sunscreen Group: Median No. of Unprotected Sun Episodes	Sunscreen Group: Median No. of Total Sun Episodes	Control Group: No. of Subjects	Control Group: Median No. of Protected Sun Episodes	Control Group: Median No. of Unprotected Sun Episodes	Control Group: Median No. of Total Sun Episodes
Face, neck, and ears	141	186.0	46.0	236.0	159	161.0	61.0	238.0
Trunk	141	208.0	0.0	216.0	159	207.0	1.0	216.0
Upper limbs	141	176.0	54.0	236.0	160	142.0	71.0	236.0
Lower limbs	141	108.0	41.5	153.0	160	95.8	53.0	145.5

dren. The pattern of association between phenotypic factors and nevus counts at induction gives reasonable assurance that the subjects are similar to those recruited for previous studies of nevi.[13,14,16] Subject retention was excellent, and parents and children exhibited a high degree of compliance in providing data on solar UV exposure during the trial. Parents in the sunscreen group provided high-quality information on the volume of sunscreen used.

No information was collected on children who elected not to participate in the trial, and it is possible that there may be some differences between participants and nonparticipants. Another potential drawback to the study is the relatively short period of follow-up; there are no clear data on the duration of solar exposure needed to initiate nevus formation. Limited data are available from the study by Harrison et al[12] demonstrating the presence of new nevi within 1 year of birth in a cohort of Australian children. Thus, the initiation period for new nevi was thought to be short, and the 3-year follow-up was anticipated to be long enough to see differences develop between the 2 intervention groups.

Another potential problem is the possibility that randomization to the sunscreen group sensitized parents of these children. If this were the case, the children's parents might have been attuned to the potential benefits of sun avoidance and might have restricted solar exposure in the children. However, reported hours spent outdoors during the 3 years of the study were similar in the 2 groups. Finally, within the intervention group, there was an inverse relationship between quantity of sunscreen used and number of new nevi, suggesting that sunscreen use was the factor of consequence in the study.

A recent study in women has demonstrated a protective effect of chemical sunscreen against CMM.[25] Most previous studies, however, have suggested either no association[26,27] or a positive relationship[28-30] between sunscreen use and melanoma risk. Furthermore, results from a recent cross-sectional study of nevi in European children suggest that sunscreen is not effective at preventing the appearance of new nevi.[31] The authors suggested that this is because use of high-SPF sunscreen promotes extended duration of sun exposure.[32] An increase in new nevi among children using sunscreen regularly was also seen in a German study.[33] Both of the European studies were well conducted but assessed sun exposure and sunscreen use retrospectively, in some cases 3 to 5 years afterward. In addition, it was not clear whether the sunscreen used in the German study was broad-spectrum and attenuated UV-A and UV-B or was primarily designed to screen out UV-B radiation. Finally, as in any retrospective investigation of nevi, incomplete control of host-susceptibility factors must be considered a potential explanation for these findings.

In our study, the reduced number of new nevi in the broad-spectrum sunscreen group suggests that these agents may be useful in preventing transformation of normal melanocytes into nevi, at least in children who freckle. As 1993 and 1996 counts were both

Table 4. Parameter Estimates for Variables Predicting Number of New Nevi in Vancouver Schoolchildren*

Independent Variable	Estimate (SE)*	*P* Value
Sunscreen group	−0.89 (4.07)	.83
Grade	6.82 (3.21)	.04
Sex	−1.51 (3.21)	.64
Freckling	0.12 (0.13)	.34
Sunscreen group–freckling interaction	−0.38 (0.17)	.03
Total sunlight exposure adjusted for clothing, 1993-1996, MEDs	0.007 (0.003)	.05
Sunburn score to age 5 years	0.30 (0.17)	.09

*Estimates generated using linear regression model controlling for grade, sex, and hair color.

Figure 2. Appearance of New Nevi Among Children by Facial Freckling

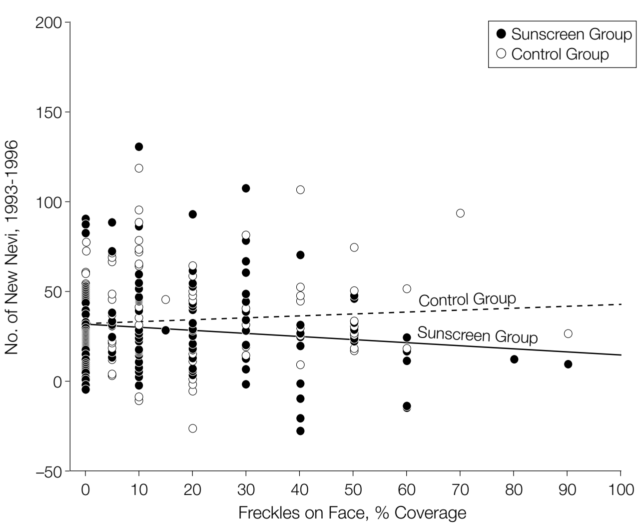
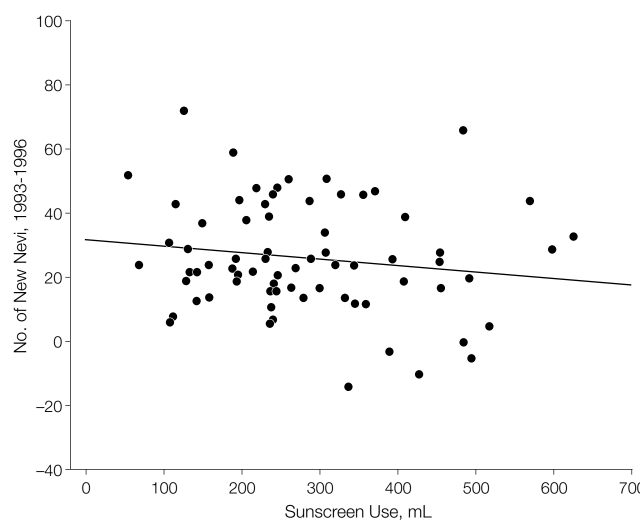


Figure 3. Appearance of New Nevi in Grade 4 Children by Amount of Sunscreen Used



conducted prior to the sunny months of the year, it is unlikely that the effect seen in freckled children was due to differential misclassification of freckles and nevi between the 1993 and 1996 counts. Both nevi[1-3,34] and freckling[35-37] are known to increase risk of CMM, and evidence suggests that nevi and freckling together have a synergistic effect on risk.[3,6] This may indicate that subjects who freckle and develop nevi have an underlying instability in their melanocytes. If so, these melanocytes might be more likely to evolve into a clone that ultimately becomes a visible nevus under the influence of solar UV radiation. Furthermore, formation of a nevus may take place with a smaller degree of solar UV damage in children who freckle than in those who do not freckle. If sunscreens protect the melanocytes, the importance of such protection against the formation of new nevi would be more important among those who freckle.

An alternative explanation for the greater importance of being in the sunscreen group for those who freckle may be found in the limited duration of the intervention. It is possible that the study saw a short-term result only in those subjects most sensitive to the development of nevi. In a trial of longer duration, a more clear-cut protective effect might be seen for all subjects, regardless of freckling status.

In summary, our findings indicate that broad-spectrum sunscreens may attenuate the development of nevi in children and perhaps ultimately reduce their risk of developing melanoma.

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