# The Simultaneous Assessment of Constitutional, Behavioral, and Environmental Factors in the Development of Large Nevi

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## Abstract

Background: **The presence of large nevi (>4 mm diameter) is the most important predictor of melanoma risk. We report on the simultaneous assessment of behavioral, constitutional, and environmental risk factors for the prevalence of large nevi in a population-based study of 33,305 individuals and compare those to risk factors for melanoma.**

Methods: **We used self-reported data from a population-based study of twins in California, assessing the prevalence of large nevi, lifetime usual sun exposure behavior and sunburn experience, skin type and color, and birthplace and recent domicile, for which we obtained estimates of potential sun exposure.**

Results: **Among constitutional variables, skin type (burn rather than tan) and having blond (but not red) hair color were associated with having more than three large nevi, as was Celtic ancestry. Spending more time in the sun in adulthood was inversely associated with number of large nevi, whereas spending time in the sun during weekends in childhood increased the risk of having large nevi. We observed no latitude gradient in nevi prevalence, except among those of Mediterranean ancestry (those in the South were more likely than those in the North to report large nevi).**

Conclusion: **The prevalence of large nevi was most readily explained by constitutional and then by behavioral variables in this study, rather than by independent variables describing an individual's opportunity for sun exposure. There seem to be independent relationships between nevi frequency and other melanoma risk factors, with the notable exceptions of skin color and red hair phenotype: implying that if these risk factors represent a genetic propensity to develop melanoma, that risk would seem to be unrelated to the development of nevi.** (Cancer Epidemiol Biomarkers Prev 2007;16(2):200–6)

## Introduction

The presence of nevi, particularly large nevi (>4 mm diameter) is the single most important predictor of melanoma risk (1-5), and the cornerstone of screening for melanoma. But it is unclear if nevi are a part of the developmental pathway for melanoma, markers of another relevant exposure (UV radiation), or reflect a genetic susceptibility in common with melanoma (6). We have previously shown that in the absence of genetic variability, there is no significant relationship between nevi and melanoma (7), and conclude that melanoma and nevi are most likely to either respond to similar genetic events, occur as a result of a common genetic predisposition, or that nevi are indeed a precursor to melanoma. Complicating the issue are the facts that nevi often occur at the same physical location as a subsequent melanoma (8), and nevus cells are often reported in melanoma specimens (9), supporting the role of nevi as precursors to melanoma.

We hypothesize that were nevi to be causally involved in the development of melanoma, they would share most, if not all, risk factors with melanoma. Were the determinants of melanoma and nevi prevalence shown to be divergent, we might consider nevi unlikely to be directly involved in melanoma development. As with melanoma, the prevalence of nevi is higher with greater sun exposure in childhood (10, 11). Hair color, skin type (measured both by its darkness and by ability to tan), and frequency of sunburn independently predict the frequency of nevi (12). However, all these risk factors are associated with both environmental (sun exposure) and genetic variation (which we refer to herein as ''constitutional factors''). Sunburn indicates not only an opportunity for sun exposure, but also a type of skin that is prone to burning rather than tanning, which itself is a combination of sun exposure behavior (a ''protective tan'') and environmental conditions. Despite the variation shown in nevi prevalence by environmental factors such as sun exposure (12), we are unaware of any previous studies that have simultaneously assessed the effect on nevi prevalence of environmental variables (sun exposure opportunity, considered here to be average weekend/weekday time spent in the sun at various ages, and number of days with no natural tan at various ages) separately from behavioral variables (considered here to be sun exposure protection activities, frequency of sunburn at various ages), and those related to constitution (considered here to be sex, hair color, the color of untanned skin, untanned skin's response to sun exposure, prior and family history of skin cancer, and birthplace of parents) that likely have genetic origins.

We have simultaneously investigated behavioral, constitutional, and environmental risk factors for the prevalence of large nevi in a population-based study whose participants were selected without reference to the prevalence of either nevi or melanoma, yet who were drawn from a population at high risk of melanoma, whose opportunity for, and activities related to, sun exposure varied greatly.

In addition to describing the complex determinants of nevi prevalence and contrasting these with known risk factors for

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melanoma, we comment on prospects for the primary prevention of melanoma based on the relative contribution of behavioral variables to nevi prevalence, and secondary prevention of melanoma based on the frequency of self-reported nevi screening activity.

## Materials and Methods

**Study Population.** This study was carried out among members of the population-based California Twin Program, established in 1990 and whose recruitment continues (13, 14). The process of recruiting participants, and the subsequent representativeness of the respondents compared with the population from which they were drawn are presented elsewhere (14, 15). Briefly, records of live multiple births in the state of California occurring between 1908 and 1982 were linked to the records of the California Department of Motor Vehicles to identify current mailing addresses. These twins were sent an introductory letter about the California Twin Program, and then mailed a 16-page questionnaire (http://twins.usc.edu/questionnaire) with a reply-paid envelope for its return. The questionnaire asked about basic demographic characteristics (age, sex, education, occupation, marital status), zygosity (16), dietary preference, disease experience (including cancer occurrence), and lifestyle choices (smoking, exercise, sun exposure). The overall crude response rate was 42.2%, and estimates of the response rate that took into account the true denominators of twins that likely received the questionnaire (removing invalid addresses) ranged from 51% to 56%. The final cohort of respondents was slightly less educated than the cohort of California-born twins, and slightly over-representative of young females among whom the response rates were the highest. Overall, we have argued that the respondent cohort is generally representative of all California-born twins and singletons, and therefore represents an excellent resource for population-based prevalence studies (14, 15).

To date, we have received responses from 41,367 individuals including both members of 11,416 twin pairs, and one member of 18,535 pairs. In this analysis, we are considering the respondents to be a population-based sample of California-born California residents. Another article will deal with the consanguinity of nevi frequency in monozygous and dizygous twins from this cohort. From the respondent cohort, we excluded those reporting races other than ''White'', and those who did not answer the question regarding nevi frequency.

*Determining Nevi Frequency and Other Nevi-Related Variables.* Participants were asked to estimate the total number of large nevi they had anywhere on their body (0, 1-2, 3-9, 10 or more), that they had had ''as long as they could remember.'' ''Large'' was defined as >4 mm, or the size of an eraser on the end of a pencil and respondents were supplied with such a pencil for filling in their questionnaires. We defined nevi >4 mm as ''large'' based on the increased risk for melanoma with nevi >4 mm in previous studies (5, 17, 18). Respondents were also asked about the frequency of skin examinations (never, sometime in past 10 years, sometime in past year), and the occurrence of skin cancer or melanoma in themselves or in other family members, but these reports were not able to be verified with medical records.

**Exposure Variables.** A variety of variables were considered in this analysis, all of them previously shown to be risk factors for melanoma.

*Constitutional and Demographic Variables.* As well as reporting natural hair color and the color of their untanned skin, we asked participants to report their untanned skin's response to half an hour of sunbathing at noon (''get a painful sunburn that blisters or peels'' to ''show no sign of sunburn''), and to gradually increasing sun exposure with no ''protective'' tan (''no sign of sunburn'' to ''painful sunburn that blisters/peels''), or with increasing sun exposure and no evidence of burning (''develop a deep tan'' to ''show no sign of tanning''; ref. 19). Participants recorded their number of years schooling, and that of each of their parents (<12, 12, and >12 years), and the country of birth of each of their parents, categorized here as Scandinavian/Western European (''Celtic''), Mediterranean/African/Caribbean/South American (''Mediterranean''), and Other (predominantly United States).

*Sun Exposure Variables.* We asked respondents to tell us about their usual sun exposure duration in weekends (<1, 1 h or more) and weekdays (<1, 1-3, 3 h or more) at ages 10, 18, and currently, and the number of summer days (0, 1-9 or more) at each of these ages they would spend in the sun with no natural tan to protect themselves. We asked about the frequency of painful sunburns resulting in peeling skin (0, <6, 6 or more times) before and at age 25 or older, and finally, we asked respondents to estimate the amount of protection from the sun they sought while outside (''little/none'', ''some'', ''complete'') at ages 10, 18, and currently.

*Geographic Variables.* County of birth was obtained from birth records. County of current residence was obtained by converting the zip code of current residence into counties conforming to 1990 Census definitions. Altitude of birthplace and current residence was determined from a listing of the altitude of county centroids. The State was divided into tertiles of approximately equal area delineated by latitude, and counties were assigned the appropriate tertile, referred to here as ''Northern'' (39-42 degrees North), ''Central'' (36-38 degrees North), and ''Southern'' (33-35 degrees North). We compared the nevi prevalence of those born in the North and currently living in the North with the prevalence of those born in the North and living in the South, and born in the South and living in the South. Sunshine hours, expressed as the average annual percentage of possible sunshine hours (lesser in the north) were obtained for each county. Analyses of geographic variables excluded those respondents who lived outside California.

**Statistical Analysis.** Self-reported nevi prevalence was dichotomized into 0 to 2 versus 3 or more for univariate and multivariate analyses using logistic regression with sun exposure, constitutional, and behavioral variables used as the independent variables (20). The study population includes both single- and double-respondent co-twins, the latter of whom do not necessarily represent individuals with independent risk factors for developing nevi. Therefore, all analyses were repeated with a data set consisting of all single-respondent twins, and one randomly chosen twin from the double-respondent twins.

**Correspondence Between Self-reported Large Nevi in Survey and Self-reported Large Nevi in a Comprehensive Skin Self-examination Kit.** In a subset of 446 of the twins reported here, we tested a skin self-examination kit that guided participants through a structured process of identifying nevi (as distinct from other marks on the skin), measuring their size, and describing them. In order to validate our question in the current study about nevi frequency, we compared the self-report of large nevi frequency to the results obtained to date from 129 participants reporting large nevi in the skin self-examination trial. This comparison is, by necessity, crude because the skin self-examination sought far greater detail about nevi size than the current study's prevalence question, up to 10 years had elapsed between the two measures, and some allowance had to be made for the frequency of nevi removal in order to compare the two measures. Nonetheless, we compare the two measures in the expectation that they produce similar estimates of the prevalence of large nevi.

## Results

There were 41,367 respondents to the questionnaire, of whom 34,102 reported their race as White. Of these, 797 respondents did not answer the question regarding nevi frequency, leaving 33,305 individuals for analysis. This latter group did not vary substantially from the respondent group of 41,367 by age, sex, education, or any of the variables considered here.

**Population Description.** Slightly less than half the sample (48.8%) reported having at least one nevus larger than a pencil eraser, and <3% reported 10 or more large nevi (Table 1). Past nevi removal was prevalent in 17.0% of respondents, and 39.9% had had some form of skin examination. All of the 1,310 respondents that did not answer the question regarding skin examination frequency also reported no large nevi. Self-report of skin cancers, including melanoma, occurred in 2,194 respondents (6.6%), and 6,151 (18.5%) reported a first-degree relative with either melanoma or another skin cancer.

**Relationship Between Nevi and Constitutional Variables.** Although lighter hair color was associated with having three or more large nevi, only blond hair remained statistically significantly associated after adjustment for age, sex, and personal or familial report of skin cancer, with a 1.5-fold increase in risk (Table 2). Lighter skin color was associated with the prevalence of three or more large nevi, but not after adjustment for age, sex, and hair color. An increasing propensity for untanned skin to sunburn seemed to be associated with having three or more large nevi, and whereas the magnitude of this effect was slightly reduced after adjustment, the dose-response remained. Having a skin type with no propensity to develop a tan (with further sun exposure, and no sun burn) was associated with having three or more large nevi—those with three or more large nevi were less likely to develop a deep tan (Table 2). As expected, self-reported melanoma was associated with a 3.3-fold increase in risk of reporting three or more large nevi, and the magnitude was only slightly reduced after adjustment for hair color and skin characteristics. Non–melanoma skin cancers, and familial report of melanoma were only 1.5 times more likely to be reported among those with three or more large nevi, and familial non–melanoma skin cancer was associated with only a 10% increase in the likelihood of reporting three or more large nevi, although this remained significant after adjustment

**Table 1. Description of a population-based sample of California-born currently resident twins**

| Exposure | All White respondents, $N$ = 33,305 (%) |
|---|---|
| Age | |
| 15-44 | 16,005 (48.1) |
| 45-54 | 11,233 (33.7) |
| 55 or older | 6,067 (18.2) |
| Sex | |
| Male | 15,784 (47.4) |
| Female | 17,521 (52.6) |
| Education (years of schooling) | |
| <12 | 6,129 (20.6) |
| 12 | 9,580 (32.1) |
| >12 | 14,100 (47.3) |
| Didn't answer | 3,496 |
| Moles | |
| None | 17,073 (51.3) |
| 1-2 | 10,881 (32.7) |
| 3-9 | 4,488 (13.5) |
| 10 or more | 863 (2.6) |
| Nevi removal | |
| Yes | 5,647 (17.0) |
| No | 27,658 (83.0) |
| Self-reported cutaneous malignant melanoma | |
| Yes | 368 (1.1) |
| No | 32,937 (98.9) |
| Self-reported skin cancer of any type | |
| Yes | 1,934 (15.8) |
| No | 31,371 (94.2) |
| Familial melanoma | |
| Yes | 1,595 (4.8) |
| No | 31,710 (95.2) |
| Familial skin cancer of any type | |
| Yes | 4,974 (14.9) |
| No | 28,331 (85.1) |
| Skin examinations | |
| Never | 19,482 (60.1) |
| In last 10 yr | 7,434 (23.2) |
| In last yr | 5,079 (15.9) |
| Didn't answer | 1,310 |
| Hair color | |
| Black | 5,101 (15.5) |
| Brown | 11,367 (34.5) |
| Blond | 15,426 (46.8) |
| Red | 1,064 (3.2) |
| Missing | 347 |

**Table 2. Likelihood of reporting three or more large nevi, versus zero to two large nevi, among a population-based sample of California-born currently resident twins: constitutional variables**

| Exposure | Unadjusted, OR (95% CI) | Adjusted, OR (95% CI)* |
|---|---|---|
| Sex | | |
| Female | 1 | 1 |
| Male | 0.97 (0.91-1.03) | 1.02 (0.96-1.08) |
| Hair color | | |
| Black | 1 | 1 |
| Brown | 1.17 (1.06-1.30) | 1.11 (1.00-1.22) |
| Blond | 1.61 (1.47-1.77) | 1.47 (1.34-1.62) |
| Red | 1.47 (1.23-1.75) | 1.14 (0.94-1.37) |
| Color of untanned skin | | |
| Dark | 1 | 1 |
| Medium | 1.06 (0.92-1.21) | 0.96 (0.84-1.10) |
| Milky White | 1.34 (1.18-1.52) | 1.04 (0.91-1.18) |
| Untanned skin's response to half hour sunbathing at noon | | |
| Show no sign of sunburn | 1 | 1 |
| Sometimes burn | 1.19 (1.10-1.30) | 1.13 (1.04-1.23) |
| Painful sunburn that blisters/peels | 1.46 (1.37-1.56) | 1.31 (1.22-1.41) |
| Supposing no burn, what would be the effect of gradually increasing sun exposure? | | |
| Show no sign of tanning | 1 | 1 |
| Sometimes tan | 0.93 (0.85-1.03) | 0.99 (0.90-1.09) |
| Develop a deep tan | 0.78 (0.72-0.84) | 0.91 (0.84-0.99) |
| Have you ever been diagnosed with malignant melanoma? | | |
| No | 1 | 1 |
| Yes | 3.34 (2.71-4.13) | 2.92 (2.35-3.63) |
| Have you ever been diagnosed with another type of skin cancer? | | |
| No | 1 | 1 |
| Yes | 1.52 (1.37-1.70) | 1.35 (1.20-1.52) |
| Has a family member, other than your twin, been diagnosed with melanoma? | | |
| No | 1 | 1 |
| Yes | 1.61 (1.43-1.81) | 1.48 (1.31-1.67) |
| Has a family member, other than your twin, been diagnosed with skin cancer? | | |
| No | 1 | 1 |
| Yes | 1.21 (1.12-1.31) | 1.11 (1.02-1.20) |
| Parent's birthplace | | |
| Celtic/Celtic | 1 | 1 |
| Celtic/US | 1.00 (0.79-1.28) | 0.98 (0.76-1.25) |
| Celtic/Mediterranean or US/US | 0.92 (0.74-1.13) | 0.90 (0.73-1.12) |
| US/Mediterranean or Mediterranean/Mediterranean | 0.78 (0.58, 1.05) | 0.91 (0.67-1.23) |

*Adjusted for all variables in this table that were statistically significant in univariate analysis.

for all other constitutional variables (Table 2). In both univariate and adjusted analyses, there seemed to be a modest dose-response between the prevalence of three or more large nevi and parental ethnicity, with those respondents reporting Mediterranean ancestry having fewer nevi than those reporting Celtic ancestry (Table 2). However, the dose-response was both modest and statistically nonsignificant.

**Relationship Between Nevi and Sun Exposure Variables.** Those respondents spending more time in the sun during adulthood were less likely to have three or more large nevi (Table 3). This persisted after adjustment for constitutional variables and all other sun exposure variables, but was only observed for weekday exposure, not weekend exposure (Table 3). Conversely, a greater likelihood of reporting three or more large nevi was observed for greater weekend sun exposure in childhood and teenage years, but not for adulthood weekend sun exposure—the magnitude of both remained after adjustment for constitutional and other sun exposure variables, and modest dose-response relationships were observed for childhood/teenage weekend sun exposure variables. The number of summer days spent in the sun with no protective tan moderately increased the prevalence of three or more large nevi if exposure occurred in teenage years and in childhood, but not in adulthood—although only modest dose-response relationships were observed, the magnitude, but not the significance, of these associations remained after adjustment for constitutional variables and the other measures of sun exposure (Table 3).

**Relationship Between Nevi and Behavioral Variables.** The prevalence of large nevi was related to the frequency of skin exams, with those seeking skin examinations in both the past year, and the past 10 years, 70% more likely to report three or more large nevi (after adjustment for constitutional and sun exposure variables: Table 4). Notably, those with three or more large nevi were not any more likely to have had a nevi exam in the past year than in the past 10 years. Respondents with three or more large nevi were thrice as likely to have had nevi removed (Table 4). Although seeking protection from the sun in adulthood was associated with fewer large nevi (this effect remaining after adjustment for all constitutional, sun exposure, and other behavioral variables), there was no association between nevi prevalence and protection from the sun in childhood. Frequency of painful, peeling sunburn was associated with greater likelihood of reporting three or more large nevi regardless of age of sunburn, and a dose-response relationship was observed with the number of painful sunburns that persisted after adjustment for constitutional and sun exposure variables (Table 4). There was a modest and statistically nonsignificant dose-response relationship between number of years schooling and nevi prevalence that was only observed after adjustment for all constitutional, behavioral, and sun exposure variables. However, the same relatively small effect was observed for father's education, but the dose-response was of greater magnitude and was statistically significant. There was no association between mother's education and large nevi prevalence (data not shown).

**Relationship Between Nevi and Latitude.** This study population was born at, or lived at, latitudes ranging from 33 to 42 degrees, and whereas most lived within 500 m of sea level, >10% lived at an altitude >500 m (Table 5). The prevalence of three or more large nevi was univariately associated with altitude of birthplace but the effect was small and was no longer significant after simultaneous adjustment for all other geographic variables, including county of residence (Table 6). Although a similar magnitude of effect



**Table 3. Likelihood of reporting three or more large nevi, versus zero to two large nevi, among a population-based sample of California-born currently resident twins: sun exposure variables**

| Exposure | Unadjusted, OR (95% CI) | Adjusted, OR (95% CI)* | Adjusted, OR (95% CI)† |
|---|---|---|---|
| Time on an average weekday spent in the sun (now) | | | |
| ≤1 h | 1 | 1 | 1 |
| >1 h | 0.85 (0.80-0.91) | 0.89 (0.83-0.95) | 0.87 (0.80-0.95) |
| Time on an average weekday spent in the sun (age 18) | | | |
| ≤1 h | 1 | 1 | 1 |
| >1 h | 1.03 (0.96-1.10) | 1.06 (0.99-1.14) | 1.08 (1.00-1.17) |
| Time on an average weekday spent in the sun (age 10) | | | |
| ≤1 h | 1 | 1 | 1 |
| >1 h | 1.03 (0.95-1.13) | 1.05 (0.96-1.15) | 1.06 (0.97-1.17) |
| Time on an average weekend day spent in the sun (now) | | | |
| <1 h | 1 | 1 | 1 |
| 1-3 h | 0.89 (0.83-0.95) | 0.93 (0.87-1.00) | 0.96 (0.89-1.04) |
| >3 h | 0.91 (0.84-0.99) | 0.99 (0.91-1.08) | 1.07 (0.96-1.19) |
| Time on an average weekend day spent in the sun (age 18) | | | |
| <1 h | 1 | 1 | 1 |
| 1-3 h | 1.11 (1.00-1.24) | 1.14 (1.02-1.27) | 1.20 (1.07-1.36) |
| >3 h | 1.12 (1.01-1.25) | 1.18 (1.06-1.32) | 1.23 (1.09-1.40) |
| Time on an average weekend day spent in the sun (age 10) | | | |
| <1 h | 1 | 1 | 1 |
| 1-3 h | 1.06 (0.94-1.21) | 1.08 (0.95-1.23) | 1.14 (0.99-1.31) |
| >3 h | 1.13 (1.00-1.27) | 1.14 (1.01-1.29) | 1.19 (1.04-1.36) |
| Number of summer days with no natural tan (now) | | | |
| None | 1 | 1 | 1 |
| 1-9 d | 1.06 (0.98-1.14) | 1.05 (0.97-1.13) | 1.02 (0.93-1.11) |
| 10 d or more | 1.12 (1.03-1.23) | 1.03 (0.94-1.12) | 0.89 (0.80-1.00) |
| Number of summer days with no natural tan (age 18) | | | |
| None | 1 | 1 | 1 |
| 1-9 d | 1.21 (1.10-1.33) | 1.13 (1.03-1.24) | 1.10 (0.94-1.30) |
| 10 d or more | 1.41 (1.27-1.56) | 1.21 (1.08-1.34) | 1.17 (0.96-1.42) |
| Number of summer days with no natural tan (age 10) | | | |
| None | 1 | 1 | 1 |
| 1-9 d | 1.16 (1.06-1.27) | 1.10 (1.00-1.21) | 1.03 (0.88-1.19) |
| 10 d or more | 1.38 (1.26-1.52) | 1.20 (1.08-1.32) | 1.13 (0.95-1.35) |

*Adjusted for all variables in Table 1.
†Adjusted for all variables in Table 1 and all variables in this table that were statistically significant in univariate analysis.

**Table 4. Likelihood of reporting three or more large nevi, versus zero to two large nevi, among a population-based sample of California-born currently resident twins: behavioral variables**

| Exposure | Unadjusted, OR (95% CI) | Adjusted, OR (95% CI)* | Adjusted, OR (95% CI)† |
|---|---|---|---|
| Ever had a mole exam | | | |
| Never | 1 | 1 | 1 |
| Sometime in past 10 yr | 1.98 (1.85-2.13) | 1.95 (1.80-2.11) | 1.70 (1.56-1.84) |
| Sometime in past year | 2.05 (1.90-2.22) | 2.00 (1.83-2.20) | 1.71 (1.55-1.89) |
| Have you ever had a mole removed? | | | |
| No | 1 | 1 | 1 |
| Yes | 2.68 (2.51-2.87) | 2.64 (2.45-2.85) | 2.31 (2.13-2.50) |
| How much protection when in the sun (now)? | | | |
| Complete | 1 | 1 | 1 |
| Some | 0.83 (0.78-0.89) | 0.89 (0.83-0.96) | 0.92 (0.85-0.99) |
| Little/none | 0.74 (0.68-0.81) | 0.86 (0.78-0.96) | 0.93 (0.84-1.05) |
| How much protection when in the sun (age 18)? | | | |
| Complete | 1 | 1 | 1 |
| Some | 0.98 (0.84-1.15) | 0.98 (0.82-1.18) | 0.94 (0.77-1.13) |
| Little/none | 0.91 (0.78-1.06) | 0.96 (0.80-1.14) | 0.92 (0.76-1.12) |
| How much protection when in the sun (age 10)? | | | |
| Complete | 1 | 1 | 1 |
| Some | 1.03 (0.89-1.20) | 1.03 (0.87-1.21) | 1.05 (0.88-1.25) |
| Little/none | 1.00 (0.87-1.15) | 1.03 (0.88-1.20) | 1.04 (0.88-1.24) |
| How often did you have a painful sunburn that peeled, before age 25? | | | |
| Never | 1 | 1 | 1 |
| Less than six times | 1.38 (1.23-1.56) | 1.28 (1.12-1.46) | 1.12 (0.97-1.30) |
| Six or more times | 1.84 (1.63-2.07) | 1.52 (1.32-1.75) | 1.20 (1.02-1.41) |
| How often did you have a painful sunburn that peeled, after age 25? | | | |
| Never | 1 | 1 | 1 |
| Less than six times | 1.24 (1.16-1.33) | 1.20 (1.11-1.30) | 1.19 (1.10-1.30) |
| Six or more times | 1.59 (1.43-1.77) | 1.48 (1.31-1.66) | 1.41 (1.23-1.63) |
| Years of schooling | | | |
| >12 | 1 | 1 | 1 |
| 12 | 0.97 (0.90-1.04) | 1.01 (0.93-1.09) | 1.05 (0.97-1.14) |
| <12 | 0.96 (0.88-1.04) | 0.97 (0.89-1.07) | 1.10 (0.99-1.22) |
| Years of schooling (father) | | | |
| >12 | 1 | 1 | 1 |
| 12 | 1.06 (0.98-1.16) | 1.08 (0.99-1.18) | 1.10 (1.00-1.20) |
| <12 | 1.00 (0.93-1.08) | 1.06 (0.98-1.16) | 1.15 (1.05-1.25) |

*Adjusted for all constitutional variables (Table 1) and all significant sun exposure variables (Table 2).
†Adjusted for all constitutional variables plus significant sun exposure variables and all variables in this table that were statistically significant in univariate analysis.

was observed for increasing sunshine hours for current residence and birthplace, neither was statistically significant. After adjustment for all constitutional and geographic variables, there was a moderate but nonstatistically significant dose-response relationship in our measure that combined birthplace latitude and latitude of current residence—that is, those born in the north and currently living in the north had a lower prevalence of three or more large nevi than those born in the south and currently living in the south, and those currently living at the opposite end of the state from where they were born had an intermediate prevalence.

Although there was no overall latitude gradient in large nevi prevalence, we observed a latitude gradient in large nevi prevalence among those whose father had Mediterranean ethnicity [odds ratio (OR) 2.3; confidence interval (CI), 1.1-4.6, for living in the South compared with living in the North], but not for those whose fathers had North American or Celtic ethnicity, nor for ethnicity measured by the birthplaces of both parents combined (data not shown).

**Correspondence Between Self-reported Large Nevi in Survey and Self-reported Large Nevi in a Comprehensive Skin Self-examination Kit.** Among the 119 people who answered the nevi prevalence question who also completed a detailed assessment of all nevi on their body, we found 70 (59%) agreed completely with respect to the total number of large nevi on their bodies. Eight people (7%) reported one or more additional nevi in the original question than in the subsequent detailed assessment. However, all eight of these people also reported having the same (or similar) number of nevi removed in the past 5 years. Of the remaining 41 people (34%), 29 reported only one to two more large nevi in the detailed assessment than in the original questionnaire. The remaining 12 people reported between 3 and 10 more large nevi in the skin self-examination than at the original report. Thus, we consider that all but 12 (10%) of the 119 people who reported in both instances were in reasonable agreement.

## Discussion

The prevalence of large nevi was most readily explained primarily by constitutional and then by behavioral variables in this study, rather than by independent variables describing an individual's opportunity for sun exposure. Among the important constitutional factors, skin characteristics confounded the univariate association between red hair color and large nevi prevalence. Skin color itself was unimportant; rather it was the skin's propensity to burn, coupled with an inability to develop a deep (protective) tan regardless of the propensity to burn that was related to a greater frequency of large nevi. Whereas both a propensity to burn and the ability to develop a deep tan indicate some attempt to seek sun exposure, or some other form of heightened sun exposure, these observations were independent of all measured sun exposure variables. Others have found that in children, light skin color was related to greater nevi prevalence independently of other constitutional factors (10, 11), but potential confounding by sun exposure in those instances was not assessed.

Our previous observation (7), that the role of nevi (the strongest independent risk factor for melanoma) is most likely mediated by genetics, can perhaps be extended to a population-based setting because here we found constitution to be the strongest independent determinant of the presence of large

**Table 5. Distribution of geographic variables among a population-based sample of California-born currently resident twins**

| Exposure | Birthplace | Current residence |
|---|---|---|
| Latitude (degrees)* | | |
| Northern (39-42) | 6,182 (18.6) | 9,280 (27.9) |
| Central (36-38) | 10,767 (32.3) | 9,068 (27.2) |
| Southern (33-35) | 16,356 (49.1) | 14,957 (44.9) |
| Altitude (m) † | | |
| 0-200 | 14,635 (47.6) | 15,393 (51.5) |
| 201-500 | 12,669 (41.2) | 8,819 (29.5) |
| >500 | 3,457 (11.2) | 5,693 (19.0) |
| Missing ‡ | 2,544 | 3,400 |
| Sunshine hours as a percentage of those annually possible for the county§ | | |
| 69% and lower | 6,129 (19.9) | 6,711 (22.4) |
| 70-79% | 23,131 (75.2) | 20,550 (68.7) |
| 80% and higher | 1,501 (4.9) | 2,644 (8.8) |
| Missing ‡ | 2,544 | 3,400 |

*Determined by the latitude of the population centroid of the county.
†Determined by the altitude of the population centroid of the county.
‡Includes out of state, and new zip codes that did not match the translation from county to zip code schema.
§Based on the average sunshine hours as a percentage of the total number possible for the county of birth/residence.

nevi. However, in this study, there also seemed to be significant and complex effects of sun exposure behavior on large nevi prevalence, which together with constitutional effects, leads us to conclude that large nevi could well be determined by a genetic predisposition that is ''turned on'' by sun exposure. This may help explain not only the discrepancy between the attributable (low) and relative (high) risk of large nevi in melanoma, but also the complex relationship between sun exposure, nevi, and melanoma.

We saw a complex picture of the role of sun exposure at various ages in the development of large nevi emerge, but it is one that is consistent with the role of sun exposure in the development of melanoma. After allowing for constitutional variables, childhood weekend sun exposure (which we might consider ''recreational'' or ''sporadic'') was associated with a greater prevalence of large nevi in adulthood, but adulthood weekend sun exposure had no effect on large nevi prevalence. Conversely, common (i.e., weekday) sun exposure in adulthood protected against large nevi development but similar exposure in childhood had no effect on large nevi occurrence. We saw similar results for ''time spent in sun in summer with no protective tan'', in which there was a dose-response relationship only for childhood exposure, not adulthood exposure.

We did not observe any overall latitude gradient in large nevi prevalence. Other studies have noted that people living closer to the equator, especially children (10), or adults who lived close to the equator in childhood (12), have higher nevus counts than those living further away and that whereas there is some effect modification by skin type (tanning ability) and hair color, an independent effect of latitude remains. Although erythemal UV varies with both altitude and latitude (21), we likewise saw no gradient in the prevalence of large nevi by either birthplace or residence altitude. In Australia, nevi prevalence in children varies within latitudes ranging from 19 to 38 degrees (10, 12). The latitudes we consider here are 35 to 42 degrees, closer to the equator, and therefore experiencing higher erythemal UV than one previous study (12), but a smaller range of latitudes to the Australian study (10). The latter study assessed latitude of place of birth but not variation in the ancestry of the White population studied. Even though we had relatively few non–North American ancestries represented here, we observed a strong latitude gradient only among those whose parents were born in Mediterranean countries, which is the group most likely to be of similar ancestry with those in the Australian study. Our data do not provide support for the existence of a latitude gradient in nevi prevalence over and above that which can be explained by the distribution of people of differing ethnicity and constitution, of which the latter is the most important. The overall lack of an association between nevi development and latitude of birth, along with the importance of childhood sun exposure reaffirm that it is personal behavior, rather than the opportunity for sun exposure, that dictates large nevi prevalence after we allow for varying constitution.



**Table 6. Likelihood of reporting three or more large nevi, versus zero to two large nevi, among a population-based sample of California-born currently resident twins: geographic variables for birthplace and current residence**

| Exposure | Unadjusted | | Adjusted* | |
|---|---|---|---|---|
| | Current residence, OR (95%CI) | Birthplace, OR (95%CI) | Current residence, OR (95%CI) | Birthplace, OR (95%CI) |
| Latitude (degrees) | | | | |
| Northern (38-42) | 1 | 1 | 1 | 1 |
| Central (36-38) | 0.97 (0.90-1.05) | 0.94 (0.86-1.03) | 1.00 (0.91-1.10) | 0.99 (0.89-1.12) |
| Southern (33-36) | 1.04 (0.97-1.12) | 1.03 (0.96-1.12) | 1.02 (0.92-1.12) | 1.01 (0.89-1.14) |
| Altitude of county seat (m) | | | | |
| 0-200 | 1 | 1 | 1 | 1 |
| 201-500 | 1.03 (0.96-1.11) | 1.10 (1.04-1.18) | 1.04 (0.94-1.15) | 1.10 (0.99-1.22) |
| >500 | 1.01 (0.93-1.10) | 1.02 (0.92-1.13) | 0.92 (0.83-1.03) | 0.97 (0.85-1.10) |
| Sunshine hours as a percentage of those possible | | | | |
| 69% and lower | 1 | 1 | 1 | 1 |
| 70-79% | 0.98 (0.91-1.06) | 1.04 (0.97-1.13) | 0.95 (0.88-1.04) | 0.99 (0.90-1.10) |
| 80% and higher | 1.11 (0.98-1.25) | 1.10 (0.95-1.28) | 1.16 (0.98-1.38) | 1.13 (0.91-1.41) |

| Exposure | Unadjusted, OR (95% CI) | Adjusted, OR (95% CI) † |
|---|---|---|
| Birth latitude versus residence latitude | | |
| Born South, live South | 1 | 1 |
| Born South, live North | 1.04 (0.94-1.16) | 1.05 (0.95-1.17) |
| Born North, live South | 1.00 (0.88-1.13) | 0.96 (0.84-1.10) |
| Born North, live North | 0.90 (0.81-1.00) | 0.91 (0.82-1.02) |

*Adjusted for age, sex, and all other variables in the table (birth variables adjusted for other birth variables, residence variables adjusted for other residence variables. Birth not adjusted for residence and vice versa).
†Adjusted for all variables in Table 2.

In this study, we observed independent relationships between nevi frequency and other melanoma risk factors, as have others (4, 8, 12, 22). Yet there are striking differences between known risk factors for melanoma and the factors apparently responsible for the prevalence of large nevi in this study. The single most important risk factor for the development of melanoma aside from the prevalence of large nevi is hair color, with red hair conveying the greatest risk, and blond hair conveying greater risk than brown or black hair (5, 17, 18, 23). In this study, although blond hair color distinguished between few and many large nevi, after allowing for all other constitutional variables related to skin type and color, red hair color was not associated with nevi prevalence. We concur with others who have shown no apparent increased prevalence of nevi (large or otherwise) with red hair color (10-12). The red-headed phenotype confers a risk of melanoma independent of sun exposure (5, 17, 18). If red-headedness represents a genetic propensity to develop melanoma, that risk would seem to be unrelated to the development of nevi.

In order to assess the accuracy of reported nevi prevalence, we compared self-reported nevi prevalence in this study with another self-report in 119 individuals who have subsequently completed a far more complex assessment of their nevi. These two self-reports did not produce substantially different counts of large nevi—after allowing for nevi removal between the two assessments, and the potential that more nevi may have developed in the interim (up to 10 years had elapsed between the assessments, so we consider that during that time, one or two new large nevi could well have developed), 90% of the respondents' counts of large nevi from the detailed assessment agreed with their response to the earlier crude question: ''how many moles larger than a pencil eraser do you have?''. Although we did not verify nevi counts in either case with professional assessment, we were able to replicate the direction and magnitude of the findings of others who used more complex measures of nevi frequency, with respect to nevi frequency and skin cancer/melanoma (22, 24). Misclassification of nevi size and counts in this study would most likely have resulted in bias towards the null, so that the effects we have highlighted likely underestimate the true associations.

Our findings have implications for the secondary prevention of melanoma which focuses on skin self-examination, or screening for skin cancer precursor lesions. People with large nevi were more likely to have had a skin exam to investigate those nevi. This bodes well for interventions aimed at educating further about nevi examination in the prevention of melanoma. However, those with more large nevi were no more likely to have had a recent (implying regular) skin exam rather than one in the past 10 years. In both these instances, it is possible that the observed association represents causation in the other direction—those people more likely to have skin checks and nevi removed are more likely to report large nevi.

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