THE EPIDEMIOLOGY Of ACQUIRED MELANOCYTIC NEVI
A Brief Review

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Malignant melanoma incidence has risen markedly over the past 30 to 40 years and continues to increase in the United States, Canada, Australia, and Europe.[11, 24, 30, 31] The tumor is rapidly becoming a major public health concern, particularly in areas that have high sun exposure.[32]

When the magnitude of the problem began to become evident, a number of studies were initiated to attempt to elucidate the etiology of cutaneous melanoma.[6, 7, 19, 22, 23, 34, 35] The major risk factors detailed by these studies can be divided into three categories: environmental, constitutional, and combination factors. The major environmental risk factor for melanoma is solar ultraviolet (UV) radiation exposure, and a major body of evidence supports this relationship.[26] Constitutional risk factors for melanoma include light skin and hair color [6, 19, 22, 34] and propensity to burn rather than tan in the sun. [6, 19, 22, 34] These factors are genetically based and are unmodifiable.

Acquired melanocytic nevi and freckles (actinic lentigines, ephelides) represent the third group of risk factors for melanoma and these combine aspects of constitutional susceptibility and environmental UV exposure.[19, 22, 34]
Nevus prevalence was found to be the strongest determination of individual risk of melanoma in these epidemiologic studies, and this was later confirmed in more detailed clinical studies.[15, 21] Furthermore, as few neonates have nevi, it seemed probable that acquired melanocytic nevi arose in response to environmental exposures or some interaction between constitutional factors and environmental exposures.

Because many melanomas have histologic evidence of a preexisting nevus,[46] at least some nevi may be precursors of melanoma.[16] The study of acquired melanocytic nevi, then, may tell us a great deal about the origins of malignant melanoma.

The following review concentrates on studies of nevi in white populations. It is well known that the prevalence of melanocytic nevi is substantially lower among pigmented races than in whites,[3,36,42] and evaluation of the association between environmental factors, phenotype factors, and nevus prevalence in nonwhite populations has been largely uninformative.[14] In addition, melanoma incidence rates are much lower in non-Caucasians than in whites,[38] and detailed studies of the etiology of nevi among non-Caucasians are scarce.

Clinically Defining and Enumerating Nevi
To enumerate and study nevi, clinical criteria need to be elaborated in order to ensure valid counts. The early studies by Pack et a1 [36,37] contained no explicit clinical criteria by which nevi were enumerated, and none of the nevi were examined pathologically. Even with expert clinical judgment, a proportion of lesions that appear to be nevi on histologic examination turn out to be other lesions.[49] In most cases, it is not possible in studies of benign melanocytic nevi to obtain histologic verification of counted lesions in order to verify the validity of the clinical impression.

Because of difficulties in determining whether all the pigmented lesions are, in fact, nevi, investigators have concentrated instead on elaborating clinical criteria to make counts more reliable or repeatable. Thus in 1973, in the first large-scale study of a representative population conducted in Australia, Nicholls [5] elected to count only lesions =2 mm in diameter and "either palpable or seen to be deforming the surface architecture of the skin when viewed tangentially." These criteria would effectively eliminate freckles, exclude some legitimate macular melanocytic nevi, and might potentially include some seborrheic keratoses. Other nevus studies have adopted different criteria.[5, 29] Some recent studies have elected to count all pigmented nevi regardless of size and palpability." Although this will include junctional nevi that might have been excluded in the earlier studies, such criteria might inflate counts by failing to exclude small dark solar lentigines.
The International Agency for Research on Cancer (IARC) has recently developed a detailed protocol to standardize methods in nevus studies.[25] Even with a greater degree of standardization, however, difficulties arise within individual studies because each counter's estimate of nevi per anatomic site differs. Up to about

10% of the variation in full body counts by different counters may be due to this interobserver variation.[9,27]

Because of the many different definitions used over time in ascertaining nevus prevalence, it is difficult to evaluate whether the increase in nevus density that appears to occur when comparing studies conducted. in the 1950s and 1960s (Table 1) with those conducted more recently is in fact real. These same difficulties also render comparisons between present day nevus counts in Australian subjects versus North America and European subjects potentially troublesome.
Notwithstanding these difficulties, a great deal has been learned about the natural history of nevi and the relationship between nevi and melanoma from a series of analytic studies conducted over the past 15 years. These studies can be divided into two categories: investigations among adults and investigations among children. The objective of these analytic studies was to detail the prevalence of nevi among different populations by sex and by age and to investigate the factors associated with a high prevalence of nevi.

Analytic Studies of Nevi in Adults
Risk factors for malignant melanoma include constitutional factors such as fair skin and fair hair, propensity to burn in the sun, and sunshine exposure itself. Because nevi and melanoma are both of melanocytic origin and share several microscopic features,[17] most of the research regarding nevus density has focused on those factors that are known to be important in the etiology of cutaneous melanoma.

One of the first studies to assess risk factors for nevi in adults was that of MacKie et al in 1985.[21] A total of 432 white Scottish subjects aged 4 days through 96 years were examined. Subjects were recruited from among families of hospital personnel, sport center volunteers, and the local territorial army. The study found no associations between frequency of nevi and hair color, skin color, eye color, freckling, or propensity to bum in the sun (Table 2). Few details were given on how skin color, hair color, and propensity to burn were assessed, and it is unclear how greying hair in the older subjects was analyzed. Nevus counts were higher in women than in men at virtually all ages. Cooke et al, [5] in a study of 872 New Zealand adults, found the highest prevalence of nevi in adults aged 20 to 39 and similar prevalence rates in men and women, with no pronounced excess in either sex. Armstrong et all used the control series from the Western Australia Melanoma Study (511 subjects) to evaluate the factors distinguishing subjects with one or more raised nevi on the arms from those with no such nevi. Nevus counts were higher in women than in men and higher in younger subjects (age =24) than in those who were olden Phenotype characteristics were evaluated, and it was found that those with intermediate skin reflectance values (medium skin color) rather than high values (fair skin) had the highest nevus counts. This finding was different from that observed in melanoma studies, where those at the highest risk had the lightest skin color. Highest nevus counts were also associated with other measures of intermediate sun sensitivity and exposure, including degree of suntan on arms and number of painful sunburns both in childhood and over the 10 years prior to assessment. When the sunlight and constitutional variables were modeled, the strongest monotonic relationship with nevus density was frequency of sunburn up to age 10, suggesting that childhood sun exposure patterns are important in establishing nevus prevalence in young adults.

Another adult control series (197 subjects) originating from a study of risk factors for melanoma in the United Kingdom showed increasing nevus counts with darker hair and eye color and type 3 or 4 (less sun-sensitive) skin [10]. Because 77 of these patients had presented for dermatologic conditions other than melanoma, the authors excluded these subjects and repeated the analyses, with the results remaining essentially the same. In a study of workers at the Lawrence Livermore National Laboratory to determine factors associated with having one or more pigmented nevi > 5 mm in diameter, the presence of blonde or red hair and lighter skin color was associated with large nevi [44] ; however, neither of these associations was statistically significant. Having a parent with skin cancer or an immediate blood relative with melanoma was weakly associated with the prevalence of large nevi, although again neither association was statistically significant. Sunburns under age 21 appeared to predispose to large nevi; however, sunburns at age 21 or older were inversely associated with such nevi. The numbers of subjects with large nevi in this study was small, limiting the power to evaluate risk factors, and perhaps explaining why none of the relationships detailed previously were statistically significant.

Augustsson and his colleagues [2] in Sweden found no relationship between adult nevus counts and- propensity to bum among 310 adult subjects aged 30 to 50. Subjects who were indoor workers had higher counts than outdoor workers; however, subjects who reported more than three severe sunburns (age at sunburn was unspecified) had higher counts than those with fewer or no burns. This may suggest that exposure of unacclimatized skin to strong sunlight may be important in accounting for nevi.

A New York- study of raised nevi =2 mm on the medial and lateral arm surfaces of 1000 subjects showed no association between nevus frequency and ability to tan.[28] Sun-exposed lateral surfaces had consistently higher counts than the far less exposed medial surfaces. There was an inverse relationship between reported sun exposure and nevus counts, however, indicating that perhaps sun exposure, particularly in older subjects, may be involved in involution or disappearance of nevi as well as their genesis.

Green et al [18] in Queensland evaluated factors associated with nevi =2 mm on the arms of a series of 183 subjects recruited as an age-matched control series for an etiologic study of malignant melanoma. The presence of nevi was inversely associated with age, with a significantly higher proportion of subjects under 35 years of age having arm nevi by comparison with older subjects. The presence of nevi was positively associated with fair skin color, red hair, green or hazel eyes, propensity to burn in the sun, and propensity to freckle. Of these, however, only the association with freckling was statistically significant. Subjects reporting the highest levels of cumulative sun exposure had the lowest probability of having one or more nevi =2 mm, and this same relationship was seen in assessing total sun exposure at ages 10 to 19.
Rampen et al [41] examined 508 subjects aged 18 to 30 and counted nevi of all sizes on the anterior thoracic wall and upper abdomen, the upper back, and the lower limbs. No association was seen between these counts and propensity to burn in the sun, time spent sunbathing, or holidays in sunny climates in the 5 years prior to examination.

Perhaps the most unambiguous results are those of Richard et al.[43] In this investigation of nevi in young male subjects aged 17 to 24, strong associations between number of nevi and both frequency of sunburn and sun exposure were seen among subjects with what the authors defined as "red phenotype" (red or blonde hair, light skin, inability to tan). Similar results were seen for sun exposure among the "dark phenotype" (brown or black hair, dark complexion, no freckles, easily tanned) subjects, although no association with childhood sunburns was detected in the dark phenotype group. The subjects in this study were quite young and this may explain why results from this investigation are similar to those observed in studies of nevi in children (Table 3).

Findings related to etiologic factors related to adult nevi are somewhat contradictory, because many of the studies are conducted over broad age ranges, perhaps with cohort differences in degree of UV exposure and nevus prevalence. It has been hypothesized that sunlight may be involved in the genesis of nevi in young people [1, 28, 31] and in their disappearance in older subjects.[1, 48] Thus, the irregular effects with, for instance, number of sunburns might be because sunburns in childhood serve to induce nevi; whereas further burns in adult years actually contribute to their disappearance. The irregular association between nevus prevalence and phenotype factors such as hair and skin color as well as propensity to burn might also be explained by greater sun avoidance behavior among those who are most likely to burn.

Because nevi arise mainly in the first two decades of life, recent research has centered on the study of etiologic factors in childhood and adolescence. The rationale behind childhood studies is that the presumed etiologic events occur closer to the time of appearance of nevi and hence may be more accurately recalled. In addition, sun exposure causing involution of nevi in older subjects is not a potential confounder.

Analytic Studies of Nevi in Children
Evaluation of the etiology of nevi in children has, as with studies of adults, been aimed primarily at factors known to be associated with development of malignant melanoma. A study carried out in the Netherlands evaluated 116 children aged 6 to 9, 78 aged 10 to 13, and 133 students aged 18 to 30 (see Table 3).[40] Nevi were more frequent in male subjects and increased with age. A score derived from four variables (burning or tanning ability, eye color, hair color, and freckling) was used to evaluate complexion sensitivity, and nevi were found to be more frequent in subjects who were more sun sensitive. Sigg and Pelloni [45] in Switzerland studied 939 children aged 8 to 16 years and found increasing numbers of nevi with increasing age, light skin color, and freckling. [45] Boys appeared to develop more nevi than girls. A more detailed study among 211 Australian children aged 7 to 11 years [2O] found that light hair, skin, and eye color, as well as a propensity to burn rather than tan in the sun, was associated with higher nevus counts. A reported, history of melanoma in a first

or second degree relative was also associated with an elevated nevus count. Children with higher nevus counts also reported more sun exposure. Again as in previous childhood studies, boys had higher nevus counts than girls. Sorahan et a1 [47] studied 187 English children, 8 and 9 years of age, and found higher counts in subjects with light skin color and a family history of skin cancer. Interestingly, no relationship Was seen with skin sun sensitivity.

These studies in children all found higher nevus counts in boys than in girls and progressively increasing counts with age. None of the studies evaluated nevus density, adjusting for the different skin surface area in boys by comparison with girls and older children in comparison with younger children.

The Vancouver Mole Study [12, 13] examined nevi =2 mm in diameter among 1146 white school children aged 6 to 18 years in Canada. This study did evaluate nevus density (nevi per square meter of skin surface area) and again found whole body nevus; density to be higher among boys at all ages, although the sex discrepancy was most pronounced at younger ages (= age 12), with girls showing substantial gains in later years (ages 13-18). Nevus density increased until about age 14. Higher density was seen in subjects with light skin color, propensity to burn in the sun, and a history of sunburns in childhood. No association was observed with hair color. Nevus density also increased with degree of facial freckling. No relationship was found with sunlight exposure, but this may be due to the fact that detailed data on sun exposure covered only the 3 months prior to examination. No indications were seen of any effect of puberty on nevus density as had been suggested in some earlier studies.[29,37]

Pope and her colleagues [39] in England conducted a study of nevi of all sizes among 2140 children aged 4 to 11 years. Adjustment was made for skin surface area, and nevus density increased consistently to about age 10 to 11 in both sexes. Nevus prevalence was elevated in subjects with light skin and eye color. Subjects with red hair had substantially lower nevus density than those with either blonde or light brown hair. Sun sensitivity or propensity to burn was associated with higher counts, as was freckling and a history of sunburn. A significant association with cumulative sun exposure was also seen in this investigation. Children in the study were not old enough to permit evaluation of possible changes in counts with the onset of puberty.

An investigation conducted on the south island of New Zealand examined 349 youths aged 14 to 15 .4 All nevi =2 mm in diameter were counted, freckling was graded, and hair and eye color were noted. No association was seen between nevus prevalence and either hair or eye color. However, subjects with an increased propensity to burn showed elevated counts. A monotonic increase in nevi with severity of freckling was also detected, although no increase in nevus prevalence was seen in subjects with a history of sunburn either in the preceding summer or in the 5 years prior to examination. Subjects reporting the highest levels of sun exposure also reported high nevus prevalence. As in other studies boys had higher counts than girls, even after adjustment for potential differences in skin surface area.

Finally, two Australian studies examined nevi among children in geographic areas with very high melanoma rates. Kelly et al [27] evaluated nevi =2 mm in diameter and showed higher counts in boys than in girls. Light skin and eye color as well as freckling and a propensity to burn in the sun were associated with elevated nevus density. The study was conducted in three cities at different latitudes, and subjects of similar age showed an in crease in nevus density with decreasing (closer to the equator) latitude, supporting the hypothesis that sun exposure is important in accounting for nevus density in children.

English and Armstrong [8,9] conducted their study on 2576 Western Australian school children aged 5 to 14, and counted nevi =2 mm in diameter as well as nevi of all sizes. Counts of nevi of all sizes were found to be the most reliable, and analyses were conducted using these figures. Nevus density increased to about age 9 to 10 in these children, with higher counts again in boys. Subjects with light skin color had higher counts than those with darker skin. Hair color from black through blonde was not related to nevus prevalence; however, subjects with red hair had significantly lower counts than all other children. Propensity to burn or freckle had an irregular relationship to nevus density, with the lowest density in subjects who only blistered in the sun and never tanned (most sun sensitive) and in subjects with the highest degree of freckling. Children with little to moderate freckling, however, had elevated nevus counts. Nevi in fair-skinned subjects can be nevus prevalence in children with highest degree of freckling was not thought to be due to difficulties in recognition of nevi in these subjects. It is possible, however, that very sun sensitive children (with red hair and freckles) may avoid the sun and hence develop fewer nevi.

Commentary

Results of studies in children are more clear cut than those among adults. Nevus density increases in children up to age 9 to 14. It appears that nevus density peaks at earlier ages in geographic areas having higher ambient sun exposure, suggesting that early sunlight exposure is central in accounting for the genesis of nevi. Nevus counts appear to be higher in those with light skin color and high propensity to burn in the sun, although individuals who are prone to burning (red hair, dense freckling, very sensitive skin) may, in fact, avoid sun exposure and perhaps develop fewer nevi than might be anticipated. This explanation is supported by the observation that in low sunlight areas such as Canada and the United Kingdom, freckling and nevus density appear to have a strong direct relationship with each other, whereas in high sun areas, subjects with heavy freckling appear to have a reduced nevus prevalence. Children with extreme sun sensitivity may also have a reduced capacity to form nevi.

In general, children with a history of sunburn, and particularly blistering sunburns, have a higher nevus density than those without burns.

Most but not all studies that have investigated sunlight exposure history have found some relationship between degree of exposure and nevus density, after controlling for phenotype factors. The exceptions may be because retrospective assessment of exposure is difficult, with a substantial amount of misclassification in the data. If misclassification occurs to the same degree in all subjects (those with high and with low nevus density), it is much more difficult to detect an association between sunlight and nevi even when the association might in reality be quitestrong.

The studies published to date have been cross-sectional rather than longitudinal in nature. If it were possible to assess sun exposure, sunburn history, and other variables on an ongoing longitudinal basis among a group of children rather than retrospectively at a single point in time, many of the associations seen in studies conducted to date might be substantially stronger.

Finally, of course, the nevus counts presented in even the most detailed studies cannot be confirmed using biopsies. As long as the error rates in counting are similar in different phenotype or sun exposure groups, however, this will not be a source of error in determining the etiology of nevi.

Conclusion

If nevi are primarily brought about by the interaction of constitutional factors with sun light exposure, it is possible that a reduction in sun exposure, particularly in sun-sensitive subjects, may reduce the number of nevi developing in children. Preexisting nevi are present in a substantial proportion of adult melanomas, and this suggests that many melanomas originate in nevi. If it were possible to reduce the nevus density of a cohort of children, this may mean substantially lower melanoma rates in this cohort as it moved into adulthood. Further studies of childhood nevi, then, should concentrate on evaluating whether a reduction in overall sun exposure, or in certain types of exposure (strong doses on sensitive skin resulting in sunburn), might attenuate increases in nevus density in children.

Further research is also needed to investigate whether broad-spectrum sunscreens might be useful in decreasing the rate at which children acquire nevi.

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Table 1. SELECTED STUDIES OF NEVI IN WHITE POPULATIONS, ALL AGES, 1950 TO 1985

Authors	Study Location	No. of Subjects	Source of Subjects	Age Range, *y*	Nevus Size, *mm*	Anatomic Sites	Nevus Counts: Selected Ages	Nevus Counts: All Ages
Pack et al,[37] 1952	New York	1000	Hospital outpatients	"Adult"	All	None excluded		14.6 (mean)
Stegmaier and Becker,[49] 1960	Chicago	20	Student volunteers	20–25	All (histologically confirmed)	None excluded	20–25 = 41 (mean)	—
Nicholls,[33] 1973	Australia	1518	Not stated	5–69	≥2	None excluded	Male age, 30–39 = 18 (mean) Female age, 20–29 = 27 (mean)	M = 18 F = 12
Cooke et al,[5] 1985	Milton, New Zealand	872	Town Health Survey	20–69	(a) ≥2	Breasts, buttocks, and genitals excluded	(a) Male age, 20–29 = 17 (mean) Female age, 20–29 = 16 (mean)	M = 15 F = 14
					(b) All sizes		(b) Male age, 20–29 = 47 (mean) Female age, 20–29 = 53 (mean)	M = 38 F = 39
MacKie et al,[29] 1985	Glasgow, Scotland	432	Nonhospital volunteers	0–96	≥3	Genital areas excuded	Male age, 20–29 = 16 (median) Female age, 20–29 = 24 (median)	— —

Table 2. ANALYTIC STUDIES OF ACQUIRED MELANOCYTIC NEVI IN ADULTS

		Trends in Nevus Prevalence with								
Study and Reference	No. of Subjects	Presence of Freckling	Lighter Eye Color	Lighter Skin Color	Lighter Hair Color	Propensity to Burn	Family History of Skin Cancer or Malignant Melanoma	Childhood Sunburns	Adult Sun Exposure	Early Sun Exposure
MacKie et al,[29] 1986	432	None	None	None	None	None				
Armstrong et al,[1] 1986	511		None	Irregular	None	None	Up	Up	Irregular	Irregular
Green et al,[18] 1986	183	Up	Down	Up	Up	Up	Down	Up		Up
English et al,[10] 1987	197		Down		Down	Down				
Rampen et al,[41] 1988	508					None			None	
Schwartzbaum et al,[44] 1990	110			Up	Up		Up	Irregular		
Augustsson et al,[2] 1992	310					None			Down	
Richard et al,[43] 1993	300			Up	Up			Up	Up	Up

Table 3. ANALYTIC STUDIES OF ACQUIRED MELANOCYTIC NEVI IN CHILDREN

		Trend in Nevus Prevalence with									
Study and Reference	**No. of Subjects**	**Lighter Skin Color**	**Lighter Hair Color**	**Lighter Eye Color**	**Propensity to Burn**	**Presence of Freckling**	**Sunburns**	**Age**	**Sex**	**Family History of Skin Cancer**	**Sun Exposure**
Rampen et al,[40] 1986	327				Up*			Up	Male ↑		
Green et al,[20] 1989	211	Up	Up	Up	Up		Up	Up	Male ↑	Up	Up
Sigg and Pelloni,[45] 1989	939	Up				Up		Up	Male ↑		
Sorahan et al,[47] 1990	187	Up			None			Up	None	Up	
Gallagher et al,[12, 13] 1990	1146	Up	None		Up	Up	Up	Up	Male ↑		None
Pope et al,[39] 1992	2140	Up	Down	Up	Up	Up	Up	Up	Male ↑		Up
Coombs et al,[4] 1992	349		None	None	Up	Up	None		Male ↑		Up
Kelly et al,[27] 1994	1123	Up		Up	Up	Up		Up	Male ↑		Up
English and Armstrong,[8, 9] 1994	2376	Up	Irregular	Up	Irregular	Irregular		Up	Male ↑		

*Rampen et al: Tanning propensity, eye color, hair color and freckling propensity combined in a single score.