

Melanoma etiology: where are we?

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Melanoma incidence rates are rising rapidly, particularly in older men. Older men are also more likely to have thick melanomas, which confer high mortality and morbidity. The reasons for the rate of increase are not known; increasing sun and UV exposure, however, is the major hypothesized explanation. In the past several years, two major susceptibility genes for melanoma, *CDKN2A* and *CDK4*, have been identified, but the two genes together account for a minority of familial melanoma. Other high-risk susceptibility genes are being sought actively. Genetic epidemiologic studies suggest that penetrance of each of the two identified genes is altered by other factors, either genetic or environmental. Epidemiologic studies have also identified other major host factors important in the development of melanoma. In European, North American, and Australian populations, the presence of clinically identified dysplastic nevi confers greatly increased risk of melanoma. A new measure of sun exposure, based on individual residential history, confers substantially increased risk of melanoma. Recent surveys of sun behavior in the US reveal extensive sunburning and use of tanning beds in adolescents and adults. Sun protective behaviors are not as prevalent as in Australia, where population rates of melanoma are stabilizing.

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Introduction

Melanoma is an epidemic cancer. The rates have steadily risen in the US and other Western countries for decades. Based on Surveillance, Epidemiology, and End Results data, it is estimated that there will be 53 600 newly diagnosed melanomas in the US in 2002, and 7400 individuals will die of melanoma. Currently, melanoma is the fifth and sixth most common cancer among men and women, respectively. The lifetime cumulative risk of developing melanoma is 1.72 for men and 1.22 for women (Jemal *et al.*, 2002). Many epidemiologic studies have been conducted of melanoma in the last 20 years to try to understand the etiology of melanoma. Major host risk factors have been identified, and the major

environmental risk factor, sun or ultraviolet exposure, has been extensively studied. This review will focus on more recent work which has contributed to our understanding of the etiology of melanoma.

Incidence and mortality patterns

Melanoma incidence varies by latitude and altitude worldwide, with areas closer to the equator and higher in altitude generally having higher rates. This pattern varies however, by the pigmentation of the population, and their sun exposure patterns. In the US and other countries, the incidence of melanoma has risen more rapidly than the mortality (Jemal *et al.*, 2000; Bulliard and Cox, 2000; Mackie *et al.*, 2002; Marks, 2002). The age-adjusted incidence rates among men are rising more rapidly than among women in the US and Australia (Jemal *et al.*, 2001; Marrett *et al.*, 2001). Incidence rates are highest among older men, and are still rising steeply in the US, Australia, and Sweden (Jemal *et al.*, 2001; Marrett *et al.*, 2001; Mansson-Brahme *et al.*, 2002). In the US, there is no evidence of a decline in incidence overall (Jemal *et al.*, 2001), but in Australia, there is some evidence of a stabilization to decrease in rates (Marrett *et al.*, 2001). In the US, for all ages combined, incidence rates increased significantly between 1988 and 1997 for all thicknesses of melanoma for each gender, except for thick (4+ mm) melanomas among females (Jemal *et al.*, 2001). Rates increased most among thick melanomas in males, particularly older males. The increases were larger in areas with less ambient UVB flux (Table 1) (Jemal *et al.*, 2000). The patterns of increase over an extended time period, and over a shorter period even in thick lesions, suggest a true increase in incidence, although some have hypothesized that the increase is due to more intensive screening or misclassification of diagnoses (Lamberg, 2002). Over time, a higher percentage of earlier lesions with a high cure rate have been diagnosed (Mansson-Brahme *et al.*, 2002; Marks, 2002).

The patterns of age-specific incidence rates in the US differ substantially among men and women (Figure 1) (SEER, 2002). The incidence is higher among young women than men, but after age 45 is higher among men. A similar pattern is seen in Sweden, but the crossover occurs about age 54 (Mansson-Brahme *et al.*, 2002). The observation of higher rates in women of reproductive

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Table 1 Increase in incidence from 1973–1977 to 1992–1996 by melanoma stage, gender, and geographic area

UVB flux and stage	Incidence per 100000 (percent increase)			
	Men		Women	
	1973–1997	1992–1996	1973–1997	1992–1996
<i>Low UVB areas</i>				
Localized	4.52	13.90 (208)	4.35	10.43 (140)
Regional/distant	1.30	2.30 (77)	0.81	1.25 (54)
<i>High UVB areas</i>				
Localized	6.94	15.98 (130)	6.79	11.04 (63)
Regional/distant	1.96	2.84 (45)	1.1	0.99 (–10)

Adapted from Jemal *et al.* (2000)

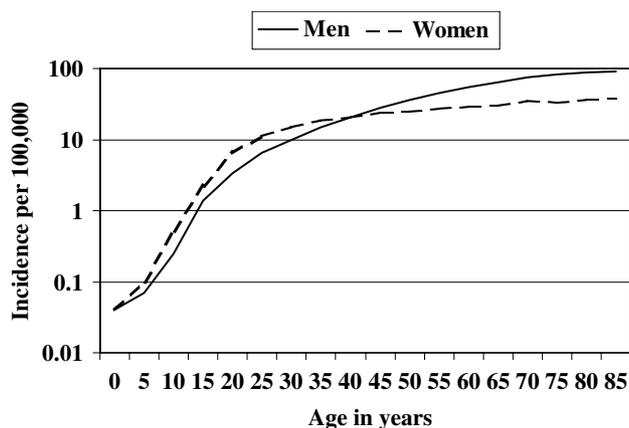


Figure 1 Age-specific incidence rates for cutaneous melanoma per 100000 for white men and women in the US from 1990 to 1999. Incidence for men in solid line; incidence for women in dashed line. SEER data from <http://seer.cancer.gov>

age has led to several analytic studies investigating the role of hormones in melanoma risk with inconsistent findings (Beral *et al.*, 1977; Holly *et al.*, 1983; Osterlind *et al.*, 1988b; Lee *et al.*, 1998; Karagas *et al.*, 2002). Among young women, incidence is increasing more rapidly than among young men (Jemal *et al.*, 2001). The causes of these age-specific differences are not known.

Mortality data are available for the entire US since 1950, in contrast to the incidence data, which are available for a selected sample of the population since 1973. From the early 1950s to the early 1990s, mortality increased by 191% for men and 84% for women. The rate of change was greatest in older men (Jemal *et al.*, 2000). The largest increases in mortality were in the northern areas. The latitudinal gradient in mortality which was pronounced in the 1950s was diminished in the 1990s. Mortality, however, was significantly higher in later time periods for both genders and all geographic areas evaluated, except for women in the west south central area (Jemal *et al.*, 2000). Jemal *et al.* estimated that the lifetime risk of melanoma mortality may have peaked for women born during the period from 1930 to 1950 and among men born between 1935 and 1950. Similar birth cohort mortality patterns have been

reported in Australia, Sweden, and New Zealand (Giles *et al.*, 1996; Jemal *et al.*, 2000). The larger fraction of thinner lesions in the later birth cohorts, and possible increased use of sun protective measures may contribute to the peaking of mortality.

Host factors

Epidemiologic studies over the past several decades have identified host factors important in risk of melanoma. These include family history of melanoma, melanoma susceptibility genes, number and type of nevi, skin type and pigmentation.

Family history

Family history of melanoma is defined differently in different studies and geographic locations. It is a complex variable, because multiple members in a family with melanoma could represent either genetic susceptibility or common exposures or both. The most common definition now is two or more first-degree relatives with melanoma, but for purposes of linkage analyses, kindreds with at least three affected family members are more informative. In general, the actual melanomas in family members are histologically indistinguishable from sporadic melanomas and have similar prognosis. Family members with melanoma, however, usually have an earlier age of onset, have thinner melanomas detected, and are more likely to develop multiple primary melanomas (Kopf *et al.*, 1986; Barnhill *et al.*, 1992). A meta-analysis of eight case-control studies from Europe, Australia, and North America revealed that family history of melanoma among individuals with melanoma varied by geographic area from 0.6 to 12.5%, with generally higher percentages in areas of higher melanoma incidence (Ford *et al.*, 1995). In this combined analysis, first-degree relatives of individuals with newly diagnosed melanoma had a two-fold increased risk of melanoma. The effect of family history was independent of nevus count, hair and eye color, and freckling. Table 2 also demonstrates percentage of melanoma cases with family history in studies from differing geographic areas assessing risk of melanoma

Table 2 Reported odds ratios of melanoma associated with dysplastic or atypical nevi and percentage of cases reporting family history of melanoma

<i>Study and variable</i>	<i>Country</i>	<i>Percent cases</i>	<i>Percent controls</i>	<i>OR (95% CI)</i>	<i>Percent cases with family history</i>
Nordlund <i>et al.</i> (1985) Atypical nevi	Australia	<i>n</i> = 296	<i>n</i> = 145	Univariate	7
0		66	93	1.0	
1-6		20	4	7.5 (3.0-18.8)	
> 6		14	3	5.8 (2.3-14.5)	
Holly <i>et al.</i> (1987) Dysplastic nevi	US	<i>n</i> = 121	<i>n</i> = 139	Adjusted	5
0		45	83	1.0	
1-5		34	14	3.8 (1.7-8.3)	
> 5		21	3	6.3 (1.9-21.5)	
Mackie <i>et al.</i> (1989) Atypical nevi	Scotland			Adjusted	
<i>Men</i>		<i>n</i> = 99	<i>n</i> = 100		3
0		64	76	1.0	
1-2		17	24	2.1 (0.9-5.0)	
≥3		19	0	4.5 (0.8-26)	
<i>Women</i>		<i>n</i> = 181	<i>n</i> = 181		4
0		61	82	1.0	
1-2		25	16	2.1 (1.2-3.6)	
≥3		14	2	4.4 (1.5- 13)	
Augustsson <i>et al.</i> (1990) Dysplastic nevi	Sweden	<i>n</i> = 121	<i>n</i> = 378	Adjusted	8
0		44	82	1.0	
1-2		27	13	2.5 (1.3-4.5)	
≥3		29	5	5.6 (2.5-12.5)	
Halpern <i>et al.</i> (1991) Dysplastic nevi	US	<i>n</i> = 105	<i>n</i> = 181	Adjusted	9
None		61	93	1.0	
Any		39	7	6.8 (2.7-16.9)	
Garbe <i>et al.</i> (1994a) Atypical nevi	Germany	<i>n</i> = 496	<i>n</i> = 476	Adjusted	3
0		63	83	1.0	
1-4		25	16	1.6 (1.1-2.3)	
≥5		11	1	6.1 (2.3-16.1)	
Tucker <i>et al.</i> (1997) Dysplastic nevi	US	<i>n</i> = 716	<i>n</i> = 1014	Adjusted	8
None		46	77	1.0	
Indeterminate		11	13	1.0 (0.7-1.6)	
1		10	5	2.3 (1.4-3.6)	
2-4		18	3	7.3 (4.6-12)	
5-9		7	1.5	4.9 (2.5-9.8)	
≥10		8	0.6	12 (4.4-31)	
Bataille <i>et al.</i> (1998) Atypical nevi	Australia	<i>n</i> = 163	<i>n</i> = 162	Adjusted	
0			85	1.0	
1			8	1.3 (0.6-2.9)	
2			2	3.9 (1.1-13.6)	
≥3			5	4.6 (2.0-10.7)	
	UK	<i>n</i> = 117	<i>n</i> = 183		
0			91	1.0	
1			5	3.0 (1.1-8.2)	
2			3	1.4 (0.4-5.9)	
≥3			1	51 (6.5-408)	
Landi <i>et al.</i> (2001) Dysplastic nevi	Italy	<i>n</i> = 183	<i>n</i> = 179	Adjusted	1.6
None		60	83	1.0	
Any		40	17	4.2 (2.4-7.4)	

associated with dysplastic nevi. In a large population-based study from Australia, Aitken *et al.* reported a higher percentage of cases with a positive family history (890 of 4633). Melanoma, however, is more prevalent in Australia and both invasive and in situ cases were included (Aitken *et al.*, 1994). Both of these factors would increase the percentage of individuals with a family history. They did find heterogeneity in melanoma risk, however, with some families having an excess compared to expected from population rates, and some families not. Overall, they identified 53 families (4.7%) at significantly higher risk of familial melanoma. Among risk factors evaluated, number of nevi was the most significant risk factor in the high-risk families.

Susceptibility genes

A number of groups worldwide have studied familial melanoma, but no one group has sufficient number of families to answer the important questions. In 1997, many of the groups who have studied familial melanoma formed the international Melanoma Genetics Consortium. The consortium was established to evaluate many of the more difficult issues in familial melanoma: the identification of susceptibility genes in addition to those already identified; evaluation of other host factors or exposures which modify risk of melanoma; estimation of the risk of other cancers associated with mutations in the genes; and the development of clinical care guidelines for these families.

Two genes conferring susceptibility to melanoma have been identified within high-risk families, *CDKN2A* and *CDK4* (Hussussian *et al.*, 1994; Kamb *et al.*, 1994; Zuo *et al.*, 1996). Both of these genes are important in controlling cell division. *CDKN2A* codes for two proteins, p16 important in the retinoblastoma pathway, and p14ARF, important in the p53 pathway. The function of these genes is discussed in the article by Hayward in this volume. Mutations in *CDKN2A* and *CDK4*, however, only account for a small percentage of families with melanoma. Aitken *et al.* (1999) found mutations of *CDKN2A* in 10.3% of a population sample of high-risk families from Australia, identified as in the study mentioned above. They estimated that 0.2% of melanoma in Australia was due to mutations in *CDKN2A*.

The likelihood of finding a mutation in *CDKN2A* is dependent on the number of affected family members overall, rising from about 5% in families with two affecteds to 20–40% in families with three or more affected individuals (Kefford *et al.*, 1999). Many of the recurrent mutations in p16 that have been described are founder mutations dating back up to 100 generations (Ciotti *et al.*, 2000; Goldstein *et al.*, 2001; Hashemi *et al.*, 2001). These founder mutations have been described in a number of different populations (Gruis *et al.*, 1995; Borg *et al.*, 1996; Platz *et al.*, 1997; Pollock *et al.*, 1998; Auroy *et al.*, 2001; Ciotti *et al.*, 2000; Goldstein *et al.*, 2001). In populations with a prevalent founder mutation, the likelihood of detecting a mutation in *CDKN2A* (frequently the founder mutation) may be higher in families with fewer affecteds than in populations with-

out such founder mutations (Soufir *et al.*, 1998; Ruiz *et al.*, 1999; Mantelli *et al.*, 2002). Population prevalence of these founder mutations have not been well quantified yet. Families with mutations in *CDKN2A* that affect only p14ARF are much less common than mutations that affect p16 with or without affecting p14ARF (Randerson-Moor *et al.*, 2000; Rizos *et al.*, 2001; Bishop *et al.*, 2002).

Recently, the Melanoma Genetics Consortium estimated the penetrance of melanoma among mutation carriers in 80 high-risk families with *CDKN2A* mutations from Europe, the US, and Australia (Bishop *et al.*, 2002). Overall, the cumulative risk of melanoma at age 50 was 0.30 and at age 80 was 0.67. The penetrance at age 80 was much higher in Australia (0.91) and the US (0.76) than in Europe (0.58). The penetrance was not altered by gender or whether the mutation altered p14ARF. Residence in an area with high population rates of melanoma, however, did significantly affect the penetrance. This suggests that factors affecting the rates of melanoma within the population affect the probability of developing melanoma among mutation carriers. Those interacting risk factors could reflect gene–environment or gene–gene interactions. Identification of these modifying factors is being pursued by the Melanoma Genetics Consortium.

Most melanoma-prone families have an excess risk primarily of melanoma, but some variants exist. Among a subset of families with *CDKN2A* mutations, there appears to be an excess of pancreatic cancer (Goldstein *et al.*, 1995; Ghiorzo *et al.*, 1999; Borg *et al.*, 2000; Vasen *et al.*, 2000; Lynch *et al.*, 2002). The risk of pancreatic cancer does not seem to be mutation-specific; among families with the same founder mutation in *CDKN2A* some families do and other families do not have pancreatic cancer. In these families, there is no identified phenotype predictive of increased risk of pancreatic cancer. The complexity of the relation between pancreatic cancer and *CDKN2A* mutation has led to the hypothesis that pancreatic cancer may not be due to *CDKN2A* mutation, but to other genetic or environmental factors. The pattern of pancreatic cancer seen in families could be consistent with another gene in linkage disequilibrium with *CDKN2A*, or other gene–gene or gene–environment interactions. Again, since no one group has sufficient families to address these questions, the Melanoma Genetics Consortium is planning to collaborate on evaluation of risks of pancreatic cancer. Breast cancer has also been reported to be in excess in Swedish melanoma-prone families with a founder *CDKN2A* mutation (Borg *et al.*, 2000). Among the families with mutations that affect p14ARF and not p16, there may be a different spectrum of tumors, including neural tumors (Randerson-Moor *et al.*, 2000; Rizos *et al.*, 2001).

The findings of variable penetrance for melanoma in different geographic areas directly inform another of the Melanoma Genetics Consortium goals of developing clinical care guidelines for high-risk families. The Melanoma Genetics Consortium has followed the ASCO clinical genetic testing guidelines (American

Society of Clinical Oncology, 1996), which suggest that clinical genetic testing only be performed for individuals who have a personal or family history suggestive of a cancer susceptibility condition, in the context of adequate education and counseling, when the risk of disease is predictable, and knowledge of mutation status would alter clinical care. In 1999, the consortium concluded that clinical genetic testing for *CDKN2A* was premature, since the penetrance of mutations was unknown and knowledge of mutation status would not alter clinical care (Kefford *et al.*, 1999). With the publication of the varying risks in different geographic areas, this question was readdressed by the consortium (Kefford *et al.*, 2002). In most circumstances, genetic testing for *CDKN2A* for clinical care is still considered premature; clinical care for members of melanoma-prone families can usually be delivered independent of clinical genetic testing.

The data for penetrance of melanoma for mutations in *CDK4* are much sparser, since few families have been identified (Zuo *et al.*, 1996; Soufir *et al.*, 1998). Goldstein *et al.* (2000b) estimated risk of melanoma among gene carriers and found no significant differences between gene carriers of *CDK4* and *CDKN2A*. This is of particular interest since *CDKN2A* is a tumor suppressor and *CDK4* is an oncogene. The age at onset, number of separate primary melanomas, and risk of melanoma were quite similar (Goldstein *et al.*, 2000b). Among two identified *CDK4* families, direct assessment of the penetrance was 63% (95% confidence interval 42–85%). Dysplastic nevi did not strongly cosegregate with mutations within these families (Goldstein *et al.*, 2002).

Variations in other genes have also been associated with increased risk of melanoma, particularly *MC1R* (see Hayward article). *MC1R* and other pigmentation genes are under active investigation, both in family and in larger population epidemiologic studies. *MC1R* variants have been associated with increased risk of melanoma in some melanoma-prone families with *CDKN2A* mutations (Box *et al.*, 2001; van der *et al.*, 2001). Based on relatively small numbers, *MC1R* variants have also been associated with increased risk of melanoma (over phenotype only) among individuals with dark complexions (Palmer *et al.*, 2000). There is some suggestion that among individuals with red, reddish-brown, or blond hair, *GSTM1 null*, *GSTT1 null*, and *GST null* may increase risk of melanoma (Kanetsky *et al.*, 2001). DNA repair genes are also of great interest both in family studies and in larger population studies. Several groups are also attempting to localize genes for nevi.

Number and type of nevi

Virtually, every epidemiologic study that has assessed number of nevi has identified nevi as a risk factor for melanoma. There has been great heterogeneity in the methods of counting nevi, from self-assessment to interviewer counting raised nevi on the arms, to full body exams by trained clinicians (Osterlind *et al.*, 1988a;

Aitken *et al.*, 1994; White *et al.*, 1994; Tucker *et al.*, 1997). Consistently, however, increased number of nevi confer increased risk (Bliss *et al.*, 1995). Fewer studies have assessed types of nevi (common versus atypical or dysplastic), and very few have had power to disentangle effects of types of nevi. When that has been possible, increased numbers of small and large banal nevi confer moderately elevated risks, in the range of two- to four-fold increase (Tucker *et al.*, 1997). These risks are of the same order of magnitude as sun-related risk factors.

Dysplastic or atypical nevi were first described in American melanoma-prone families (Clark *et al.*, 1978; Lynch *et al.*, 1978). They also occur frequently in melanoma-prone families from the Scotland (MacKie, 1982), Netherlands (Bergman *et al.*, 1992), England (Newton-Bishop *et al.*, 1994), Australia (Ang *et al.*, 1998), Sweden (Hashemi *et al.*, 1999), Italy (Landi *et al.*, 1999), Spain (Ruiz *et al.*, 1999), and France (Chaudru *et al.*, 2001). At present, although it was initially hypothesized that dysplastic nevi and melanoma were pleiotropic effects of a single gene (Bale *et al.*, 1986), the majority of data suggest that dysplastic nevi are independent risk factors for melanoma. Presence of dysplastic nevi does not appear to cosegregate with mutations in *CDKN2A* or *CDK4* (Puig *et al.*, 1997; Goldstein *et al.*, 2000a, 2002; Chaudru *et al.*, 2001). The natural history of dysplastic nevi and melanoma does not appear different in families with identified *CDKN2A* mutations, *CDK4* mutations, or no identified mutations in *CDKN2A* or *CDK4* (Tucker *et al.*, 2002). In both melanoma-prone family members (Tucker *et al.*, 2002) and in unselected individuals with dysplastic nevi (Halpern *et al.*, 1993a), the majority of lesions are stable over time or regress. The Melanoma Genetics Consortium is currently collecting consistent phenotype data across multiple groups to evaluate dysplastic nevi as a modifier of risk of melanoma associated with mutations in melanoma susceptibility genes.

Dysplastic nevi have been somewhat controversial since first described, and variant characteristics have been used by different groups for both the clinical and the histologic diagnoses of these lesions. Among clinicians who agree on clinical criteria, there is high correlation of the diagnosis (Hartge *et al.*, 1995). Among a panel of international melanoma pathologists, criteria for the diagnosis of dysplastic nevi were agreed upon. The mean concordance overall for a review of 114 mixed (radial growth phase melanoma, dysplastic nevi, banal nevi) specimens was 92% (Clemente *et al.*, 1991). Even among general dermatopathologists, there was high concordance with melanoma specialists in the reading of dysplastic nevi (Weinstock *et al.*, 1997). The data from epidemiologic studies are compelling that these lesions, no matter what they are called, are associated with greatly increased risk of melanoma (Table 2). Most risks in epidemiologic studies refer to the clinical, not the histologic diagnosis of dysplastic nevi. Even with somewhat variable defining criteria, the risks are remarkably consistent in diverse high- and low-risk populations (Table 2). In most of the reported studies, dysplastic nevi occur in a high percentage of melanoma cases. An

accurate attributable risk has not been estimated. Data from both prospective clinical and cohort studies are also consistent with greatly increased risk of melanoma in individuals with dysplastic nevi (Rigel *et al.*, 1989; Halpern *et al.*, 1993b; Kelly *et al.*, 1997).

The etiology of nevi is not well characterized, but multiple groups are pursuing these questions. Most studies have focused on banal nevi rather than dysplastic nevi. Trials of solar protection in children and adolescents have shown that adequate protection decreases the number of new nevi developing (Gallagher *et al.*, 2000; Milne *et al.*, 2002). Children in Australia with increased numbers of nevi had more sun exposure than those with fewer nevi (Harrison *et al.*, 1994) and were more likely to have been sunburned. Surveys of nevus number in children, adolescents, and adults are also consistent with solar and ultraviolet exposure contributing to the etiology of nevi (Kelly *et al.*, 1994; Harrison *et al.*, 1999; Karlsson *et al.*, 2000; Wachsmuth *et al.*, 2001; Darlington *et al.*, 2002). Analysis of two case-control studies of melanoma evaluating risk factors for nevi also showed evidence of a role of sun exposure in nevus and atypical nevus development (Stierner *et al.*, 1991; Garbe *et al.*, 1994b; Breitbart *et al.*, 1997 [Garbe and Breitbart different analyses of same data set]). In the Swedish study, the distribution of common nevi was consistent with intermittent sun exposure, but the distribution of dysplastic nevi was not. A role for sun exposure as important in nevus and atypical nevus development and perhaps change is consistent with the concept of dysplastic nevi and nevi as intermediate end points in melanoma tumor progression (Clark and Tucker, 1998). Differential patterns of nevus distribution in highly sun protected boys and girls suggest a possible role for hormones (Kwan *et al.*, 2000). There is also evidence of some genetic component of risk of common nevi in twin studies (Zhu *et al.*, 1999; MacGregor *et al.*, 1999; Bataille *et al.*, 2000; Wachsmuth *et al.*, 2001), but no major gene conferring increased risk has been identified. It is likely that the etiology of nevi is complex, varies by nevus type, and is due to the interaction of multiple genes and environmental factors. Understanding the etiology of nevi, and the changes in nevi during tumor progression, however, may well be the next important advances in melanoma etiology.

Skin type and pigmentation

Early on, it was recognized that fair-skinned individuals were more likely to develop melanoma than more darkly pigmented individuals. Virtually all epidemiologic studies find pigmentation to be a risk factor for melanoma. In a meta-analysis of 10 case-control studies, there was a gradient of risk from black or dark brown hair to red hair, with red hair conferring a two-fold increased risk (Bliss *et al.*, 1995). These risks were not altered by adjustment for freckling, nevus number, or skin color. In the same meta-analysis, light eyes conferred a 50% increased risk, which disappeared after adjustment for freckling. Light skin color also conferred

approximately a twofold increased risk, which did not change with adjustment for hair color, freckling, or nevus number. Extensive freckling was associated with a twofold risk, also. The effect of freckling appeared stronger in younger individuals, risking to a threefold increase in those under age 40.

One of the persistent difficulties in assessing skin color has been a consistent measurement within studies and across populations. Ability to tan, rather than color of unexposed skin, may be a better risk marker for melanoma (Armstrong and Kricke, 2001; Fears *et al.*, 2002).

In a recent case-control study in Italy, unexposed skin color was assessed with a colorimeter. Brightness of constitutive skin color and minimal erythral dose were both related to risk of melanoma in this more deeply pigmented, low-risk population (Brenner *et al.*, 2002).

Another approach has been the correlation of skin and hair color with the extraction and quantification of eumelanin and pheomelanin in undyed hair (Zanetti *et al.*, 2001). This has promise for more consistent quantification of pigmentation in large studies. Preliminary studies show correlations of cutaneous melanin density and number of nevi (Dwyer *et al.*, 2000). These measures have not yet been correlated with *MC1R* genotype.

Sun and other UV exposures

Sun and ultraviolet radiation exposures are the major environmental risk factors for melanoma. The epidemiologic data implicating sun exposure have recently been reviewed (Elwood and Jopson, 1997; Armstrong and Kricke, 2001). Measurement of sun exposure by questionnaire is quite difficult and data are not necessarily reproducible, especially with respect to intermittent exposures or sunburns (English *et al.*, 1998). In a meta-analysis of up to 29 case-control studies, intermittent (recreational or vacation) exposure was associated with an odds ratio (OR) of 1.71 (95% CI 1.54–1.90); occupational sun exposure OR = 0.86 (95% CI 0.77–0.96); and total exposure OR = 1.18 (95% CI 1.02–1.38). Sunburns at any time of life conferred indistinguishable almost twofold increased risks (Elwood and Jopson, 1997). Sunburns are a complex measure of both host susceptibility and exposure (as are freckles). Individuals who burn badly as children frequently reduce exposure (and likelihood of burning) as adults. In most epidemiologic studies, there are few individuals who did not burn as a child, but started burning as an adult, unless they were in unusual circumstances or in a different geographic location. The studies considered in Elwood and Jopson in which the intermittent exposures conferred the higher risks tended to be in populations residing in relatively low ambient UV areas, who may be more likely to vacation in sunny regions. This vacation exposure could account for a substantial proportion of their total yearly sun/UV exposure.

Based largely on migration studies, it has been hypothesized that childhood may be a particularly

susceptible time for sun exposure (Armstrong and Kricger, 2001; Whiteman *et al.*, 2001). In the Elwood and Jopson meta-analysis of timing of sunburns, there was no apparent difference in risk of melanoma among individuals who sunburned in childhood, adolescence, or as adults (Elwood and Jopson, 1997). A more recent large multinational case-control study also showed no difference in risk between sunburns in childhood (less than 15 years) and older ages (Pfalberg *et al.*, 2001). In their review of childhood exposure, Whiteman *et al.* (2001) concluded that exposure to high levels of sunlight in childhood is an important risk factor for melanoma, but sun exposure in adulthood was also important. Part of the apparent variation in results of different studies may be due to behavioral patterns. Much of an individual's total life exposure to sun is obtained in the childhood and adolescent years, because of the greater time spent outdoors in youth (Fears *et al.*, 2002). Among controls, most of the cumulative hours outdoors among individuals up to age 50 were obtained prior to age 20. Even among individuals up to 80 years of age, almost half of their cumulative hours outdoors occurred prior to age 20. The average annual hours outdoors was much less during adult years than before age 20. In addition, individuals who do not tan spend much less time outdoors as adults than individuals who do tan well and there are marked differences among men and women in exposure patterns (Fears *et al.*, 2002). All together, data are consistent with cumulative exposure being important, whether acquired as an adult or as a child. These findings imply that UV exposure is important in all stages of melanoma development from nevi through invasive melanoma, not just in the initiation of nevi.

With the limitations of possible recall bias and poor reproducibility of sun exposure measures, Fears *et al.* hypothesized that residential history might be a better measure of cumulative sun exposure. They estimated cumulative and average annual UVB flux for each study participant, based on the residential history and measurements from ground level UVB meters. A 10% increase in average annual UVB flux was associated with a 19% increase in melanoma risk among men and 16% increase in melanoma risk among women. Among men, a 10% increase in hours outdoors was associated with a 2.8% increase in risk; among women who tan well, a 10% increase in time outdoors was associated with a 5.8% increase in risk. Although overall, tanning well was protective compared to not being able to tan, among those who tan well, increased time outdoors was associated with increased risk of melanoma (Fears *et al.*, 2002). If this methodology is confirmed in other studies, it may be an extremely useful tool for assessing exposure in different populations. For the US population, total residential history may be particularly relevant; only 13% of study subjects lived in the area where they were born (Fears *et al.*, 2002). In populations with more stable residential patterns, residential history among geographically defined populations may not be as useful (Landi *et al.*, 2001).

Whether sunscreen use protects against melanoma or enhances risk is a controversial topic. In most epide-

miologic studies, use of sunscreen is highly confounded by host risk factors such as complexion, number of nevi, sun sensitivity, and time spent outdoors. Few studies have actually collected information on frequency of use, completeness of use, and type of sunscreen used. A recent meta-analysis of 11 studies that had reported sunscreen use found no significantly increased risk of melanoma, but heterogeneity between the results of the studies (Huncharek and Kupelnick, 2002). Among population-based studies, there was no heterogeneity, and no increased risk of melanoma. Among hospital-based studies, there was substantial heterogeneity and the summary risk was elevated, providing evidence of some bias. Another group reviewed the epidemiologic studies, and concluded that there was inconsistent information in the studies that did not suggest a causative relation between sunscreen use and melanoma (Bastuji-Garin and Diepgen, 2002). They also nicely summarized the shortcomings and methodologic problems in assessing sunscreen use. Among adolescents with melanoma in Australia, no or rare use of sunscreen at home under the age of five doubled risk of melanoma (Youl *et al.*, 2002). It is likely that the question of the relation of sunscreen use to prevention or risk of melanoma will not be resolved by retrospective studies which may be subject to recall and other biases. The answer may only be convincing from a prospective cohort study or clinical trial. Sunscreen is also only a part of sun protection, although it is one of the most frequently used types of sun protection in the US (Weinstock *et al.*, 2000). As mentioned above, sunscreen use in children did decrease the number of new nevi in a clinical trial (Gallagher *et al.*, 2000). This could be indicative of protection against melanoma, since melanoma risk is related to total number of nevi.

Until recently, population data about sun exposure patterns in the US were quite limited. A survey of 2324 beachgoers in southern New England assessed sun behavior practices. Among the beachgoers, 60% were female and 35% were between the ages of 16 and 24. A total of 25% had had more than three bad blistering sunburns in the past; 45% had used a tanning parlor or sun lamp (14% within the past year). Importantly, 83% did not often avoid midday sun, and only 45% often used sunscreens. Of those who used sunscreens, only half used sunscreens with an SPF of at least 15 on all exposed areas of their skin. Individuals with large moles were not more likely to use sun-protective behaviors (Weinstock *et al.*, 2000). Although this is clearly a 'sun seeking' population, many of these individuals already had substantial risk of melanoma from their exposures. Among over 100 000 adults from all 50 states surveyed by the Centers for Disease Control, 31.7% reported a sunburn in the past year; 57.5% of younger adults (aged 18-29) reported a burn in the past year (Saraiya *et al.*, 2002).

With the recognition that childhood exposure is an important component of melanoma risk, surveys have been conducted of sun and other UV exposure patterns in adolescents. In a small study of Texas teenagers assessing knowledge of melanoma risk factors and

prevention, 33% had had more than three blistering sunburns, 76% sunbathed outdoors, and 18% used a tanning bed within the past year (Lucci *et al.*, 2001). If one assumes that half of the respondents over age 16 were female, then approximately 60% of females 16–19 used tanning beds. A large national survey of adolescents aged 11–18 revealed that 72% reported at least one sunburn that summer (not necessarily blistering), and 30% had had at least three. Individuals with five or more burns were twice as likely not to use sunscreens. One in five had an average of over 4 h a day of exposure during peak hours during the summer. The most frequent activities during these exposures were participating in or watching sports or swimming and other water sports (Davis *et al.*, 2002). Another aspect of the same study assessed tanning bed/sun lamp use. Overall, 10% of those queried, and 8% of their guardians used sunbeds/sunlamps in the past year. The proportion rose to 30% among those whose guardians also used sunbeds/sunlamps, and to 40% among girls aged 17–18. Those who used sunbeds/sunlamps were more likely to spend more time at the beach, and were less likely to use sunscreens (Cokkinides *et al.*, 2002). In a much larger national survey, 40% of girls and 26% of boys reported routine sunscreen use, but sunscreen use was more frequent in younger ages and among those who were sensitive to the sun. In this sample, 83% reported at least one sunburn (not necessarily bad blistering), and 36% reported three or more burns in the past summer. Girls were more likely to be burned. Those who thought it was worth getting a burn to tan were more likely to have multiple burns. Among these adolescents, 10% had used a tanning bed within the past year. Girls were more likely to use tanning beds; the prevalence of tanning bed use in girls rose from 7% among 14-year olds to 16% among 15-year olds to 35% among 17 year olds ($P < 0.001$) (Geller *et al.*, 2002). Even among young Swedish adults from melanoma-prone families, 35% reported using tanning beds (Bergenmar and Brandberg, 2001).

These reported patterns of behavior may explain the higher rates of melanoma among young women than among young men. Adolescent girls are more likely to sunbathe, to get sunburned, to want to tan, and to use tanning beds. The rate of sunburns (over 70% of adolescents in two separate large surveys) and tanning bed use (over a third of older adolescent girls) is of great concern, and may well be contributing to the rising incidence rates in young women. In Australia, extensive public education such as Slip! Slap! Slop!, SunSmart, and Me No Fry and professional education such as the National Skin Cancer Awareness Programme, have made a large difference in knowledge of melanoma and in sun behaviors. The desire for a suntan has become less prevalent, and the rates of sunburn have decreased. As above, the increase in incidence and mortality from melanoma have slowed. Sun protection policies in schools and creation of shade in school yards are now routine (Marks, 2002). In contrast to Australia, only 3.4% of 412 elementary schools in US cities with a reported UV index had a sun protection policy. Most

outdoor activities occurred in peak sun hours from 10 am until 2 pm. Although about 3/4 had some shade structures, about 2/3 covered less than 1/5 of the grounds (Buller *et al.*, 2002). School-based sun education is in its infancy in the US. Until there is much broader public education about melanoma and sun behaviors in the US, it is likely that the rates of melanoma will continue to rise.

Future directions

The remarkable advances in the genetics of melanoma have led to much greater understanding of the etiology and the biology of melanoma. Few melanomas, however, are attributable to germline mutations in identified genes. Although additional melanoma major susceptibility genes are being actively sought, it is unlikely that germline mutations in these gene(s) will be more frequent than in *CDKN2A*. Genes conferring lower risk, with more frequent variations, will likely play an important role in melanoma etiology, also. It will take much larger collaborative studies to adequately evaluate them.

The next level of epidemiologic studies should incorporate biologic samples not only for genetic studies, but also to assess host/environmental interactions. One example of this approach was Landi's exploration of DNA repair capacity using the host cell reactivation assay and the interaction of impaired DNA repair capacity with skin sun sensitivity and with dysplastic nevi in melanoma risk (Landi *et al.*, 2002). For melanoma, because of the extensive epidemiologic studies of the last decades, we know many of the most important risk factors and exposures. We have much less understanding of the interactions of host risk factors and exposures: skin/hair pigmentation/sun sensitivity with differing sun and UV exposures; common nevi and dysplastic nevi with types or extent of sun and UV exposure, etc. Where it has been looked at, surrogates of sun exposure and presence of dysplastic nevi appear additive (Tucker *et al.*, 1997). Until we complete large studies to address these questions, we will not fully understand the mechanisms of melanoma development.

It may be possible now to consider both primary and secondary prevention strategies, since we have identified the major environmental factor for melanoma, and many host factors conferring markedly increased risk. The largest public health benefit is likely to come from enhanced sun and UV education and protection programs, both for children and adults. Decreasing sun and UV exposure would have the additional benefit of impacting the rates of the most common cancers, the nonmelanoma skin cancers. Although some high-risk groups (e.g. members of high-risk families; individuals with dysplastic nevi) have been identified, screening and prevention strategies applicable in broader populations could be more fully informed. Refining definitions of specific high-risk groups would greatly enhance secondary prevention.

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