The Current Epidemiology of Cutaneous Malignant Melanoma

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1. ABSTRACT

As a background for understanding the increased incidence of melanoma, relevant information focuses on incidence, mortality, environmental factors, host factors, and genetic factors. Incidence has increased dramatically; however, it is not clear to what extent changes in behavior, in the environment, or in early detection are involved. The major environmental factor, ultraviolet radiation exposure, shows surprisingly modest risks for developing melanoma, approximately 1.7-fold, and so focus is turning to interactions of exposure with host factors, including genetic factors. The major host factors associated with the development of melanoma include skin type and numbers of nevi (as well as atypical nevi). Genetic factors associated with familial melanoma have been well described and new attention, not yet validated, is being paid to low penetrant genes and their polymorphisms.

2. INTRODUCTION

The increased incidence of cutaneous malignant melanoma in most lightly-pigmented Caucasian populations is of great concern for public health administrators. More recently, increases have been noted among some Latin countries, such as Spain, Portugal, and among the Hispanic population in the United States. It is critical to have a clear understanding of the roles of screening pressure, sun exposure and genetic factors in this rise and so this paper is an attempt to provide the necessary background for such an analysis.

3. DESCRIPTIVE EPIDEMIOLOGY

The incidence and mortality of cutaneous melanoma have increased substantially during the last several decades among all Caucasian populations. There
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Table 1. Incidence rates for cutaneous melanoma for males and females among the highest ranked developed countries, with China and Japan for contrast, standardized to the world age structure

<table>
<thead>
<tr>
<th>Males</th>
<th>Country</th>
<th>Rate</th>
<th>No</th>
<th>Females</th>
<th>Country</th>
<th>Rate</th>
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<td>3.</td>
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<td>15.9</td>
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<td>13.3</td>
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<td>Sweden</td>
<td>13.3</td>
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<td>6.</td>
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Adapted from reference 3

are some indications of upward trends among other groups, such as Japanese and Hispanics in the United States (1, 2). Although incidence and mortality continue to rise overall, in most populations they have either fallen or plateaued among young individuals and, in particular, among females. Most observers describe a “cohort” effect in these trends, indicating perhaps that downward trends will continue in the future. The causes for these trends are not clearly understood and may include trends in attitudes and practices toward sun exposure and increased public awareness of the early warning signs of melanoma as well as improvements in skin cancer awareness among clinicians.

3.1. Melanoma Incidence

Melanoma incidence figures continue to increase in the United States and in many Caucasian populations worldwide. Melanoma is a cancer of lightly pigmented people; among populations of non-European origin incidence rates are highly variable and relatively low due to the low numbers of cases (Table 1).

3.1.1. World Incidence Rates

Incidence rates vary dramatically around the world, ranging from 0.59 per 100,000 in less developed countries to 40.5 per 100,000 among males in Australia (World Standardized Rates). A comparison of melanoma incidence rates shows wide variation even within close geographical proximity. For example, Norway’s incidence among males is 14.1 per 100,000 while Ireland’s is 7.9 per 100,000 (Table 1).

3.1.2. Age-Adjustment of Rates

All incidence data are age-adjusted to a standard reference population in order to compare rates between and among populations. The precise rate depends on the population used for age-adjustment. For example, adjusting rates to the European populations (3), the 2000 United States standard population (4), or the World population (3) all lead to different rates. In the United States, the 1998 incidence rate among males age adjusted to the world population is 13.3/100,000 (3), whereas the 1998 incidence rate adjusted to the 1970 population is 19.3 (1), and the incidence rate adjusted to the 2000 US population is 23.1 (4). Furthermore, comparison among countries is made more difficult due to the difference in level of effort expended in collecting incidence and mortality data.

3.1.3. Incidence Trends

The Surveillance, Epidemiology and End Results program (1) in the United States began collecting accurate incidence data for all cancers in 1973. Since that time, melanoma incidence has risen from 6.7 per 100,000 in males and 5.9 per 100,000 in females to a high in males of 10.4 in 1996 and in females of 14.3 in 1997 (Figure 1).

The downturns noted as of 2001 are actually artifacts (6) and are due to the late reporting of melanoma cases. In fact the rate continues to increase, once these delay-reported cases are found.

3.1.4. Cohort Effects

Increases in incidence over time seem to be due to a “cohort” rather than a “period” effect. A period effect would appear as increased incidence and mortality at one time point followed by a decrease in both incidence and mortality in all age groups simultaneously, and often reflects an historical event. On the other hand, a cohort effect appears as increased incidence and mortality among groups born at a certain time. Those individuals born prior
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Figure 1. Trends in melanoma incidence between 1973 and 2002 in the United States (1).

3.1.5. Anatomic Site

Not only does the melanoma incidence at each anatomic site (head and neck, trunk, and extremities) give insight into etiology, but the time trends may also yield clues to the causes of melanoma. In Canada between 1969 and 1993, for example, the largest relative increases in incidence occurred for the upper limbs in both sexes (7) and in New Zealand during the same time period (8), the largest increases were seen for the upper limbs in males (7.3% per year). As these analyses were not adjusted for tumor thickness, it is difficult to determine whether these increases are due to increased surveillance or a new exposure.

3.1.6. Age and Sex

Melanoma is an unusual cancer insofar as it occurs in a younger age group than other solid tumors. The mean age for diagnosis is approximately 52 years, some 10 years earlier than the more common tumors such as breast, lung and prostate.

The ratio of male:female incidence varies by latitude, appearing to be lower at higher latitudes, at least in Europe (9). However, that trend may be disappearing as incidence increases.

The time trends for melanoma incidence by age and sex show that the younger age groups may be stabilizing their rates (males) or actually declining (females) in Australia and in the United States (Figure 2). Conversely, incidence rates are continuing to increase among males over the age of 65 (10).

Assessment of incidence rates by age and sex on the logarithmic scale shows that the differences are not as great as one would think by looking at them without the transformation (Figure 2). Young women are at higher risk for developing melanoma prior to the age of 50 or so, when male incidence overtakes female. This trend is quite different in Europe where females have higher incidence than males.

It is often stated that among young women melanoma is the cancer with the highest incidence. In fact, that is not correct. Melanoma ranks second to thyroid cancer in women aged 15-24, and second to breast cancer in women 25-44 years old.

3.1.7. Tumor Thickness

Data on trends should always be adjusted for tumor thickness and this is not often done. The greatest increase in melanoma incidence is among the very thin lesions—those less than 0.76 mm. When trend data from New South Wales in Australia were analyzed by Breslow thickness (10), they showed a decrease in thick lesions (>0.75) among both males and females under the age of 65, with increases in thick lesions among those older than 65. These increases were statistically significant only for males who were 75 years or older. An actual decrease in incidence of thin lesions was found for men younger than
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Figure 2. Age and sex at diagnosis, 2002 (1).

35 and women younger than 50. All other age groups demonstrated an increase in the incidence of thin lesions. In Europe, the trends in melanoma incidence show a decrease in lesion thickness, although older individuals and men have thicker lesions. Similar patterns occur in the United States.

3.2. Mortality

Mortality rates are more than five-fold lower than incidence rates throughout the world and have plateaued or declined among some age groups. Although New Zealand and Australia have the highest mortality rates among males, the mortality rate among females in Norway is slightly higher than in Australia. Overall, females seem to have better survival than males once melanoma has been diagnosed. There is little convincing evidence as to whether this is due to behavior, such as early detection, or biology, such as less aggressive tumors.

It is clear from Figure 3 that mortality rates between 1969 and 2002 have increased rather sharply for males but very little for females. Little is known as to why males have somewhat higher incidence and mortality with melanoma in the United States and Australia. Hypotheses center on females’ greater interest in skin abnormalities and thus earlier detection, which may or may not improve mortality from melanoma. However, it would appear that not only do males suffer deeper lesions but also that males spend more time in sun-related activities. The extent to which the differences in mortality are due to solar exposure is not known.

3.3. Survival

Survival with melanoma is highly dependent on stage at diagnosis (Figure 4). Because the majority, 83% in the United States (1), of melanomas are diagnosed at a localized stage, survival with melanoma overall is very good, 90 percent five year survival (1). However, when melanoma is diagnosed at a regional or distant stage, survival is poorer as seen above – 62 percent for regional stage and 15 percent for distant stage at diagnosis. To date, treatment efficacy is uncertain, so the emphasis has been on early diagnosis, even though the efficacy of early detection has not yet been proven (11).

4. ENVIRONMENTAL FACTORS

Melanoma is one of the few cancers for which there is a clear environmental factor in its etiology. The major focus has been on sunlight but as there is no animal model for cutaneous malignant melanoma, there has not been direct evidence for the role of sun exposure – particularly in terms of wavelengths responsible for initiation and those responsible for promotion.

4.1. Sunlight

Sun exposure is generally equated with ultraviolet radiation exposure, although the evidence does not rule out other unmeasured exposures associated with the sun. The alarming rise in skin cancer incidence has lead to numerous attempts to explain why there has been such an increase. In the public mind, a major correlation exists between increased outdoor activity and increased skin cancer rates. In fact, there are no data available to substantiate such a relationship; that is, although there has been a dramatic increase in melanoma incidence over the last 50 years, no data show that has been an increase in outdoor activity during the past 50 or so years although the trend toward wearing less clothing is self evident.

The data to support an association between sun exposure and the development of melanoma are indirect. There has been a latitude gradient for the incidence of melanoma among Caucasians, such that the highest rates
are nearest the equator. In Europe this gradient has been confounded by the fact that those with darker pigmentary phenotype live in the Southern areas of Europe and those with lighter phenotype in the Northern, so that the gradient in Italy, for example, was actually reversed. However, this does not explain the higher melanoma rates in Norway than in Sweden. Furthermore, new data suggest that trends for incidence and mortality are “evening out” in terms of latitude. Armstrong and Kricker (12) estimate that between 68 and 90 percent of all melanomas are caused by sun exposure. Most would not dispute this estimate; however, the major point here is that it is likely intermittent sun exposure among susceptible individuals that leads to melanoma.
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It is a surprise to many that analytic epidemiologic studies have shown only modest risks at best for the role of sun exposure in the development of melanoma incidence, and two recent systematic reviews have demonstrated extremely similar estimates of effect for the role of intermittent sun exposure, an odds ratio of 1.57 (13, 14). It is important to note that chronic sun exposure, as in those occupationally exposed to sunlight, is protective for the development of melanoma, with an odds ratio of 0.70, equivocal for the development of basal cell carcinoma, and a risk factor for squamous cell carcinoma. These studies show odds ratios ranging from 0.6 to 8.4 for intermittent sun exposure, with a summary odds ratio of 1.71 (95% CI 1.54-1.90). As Elwood and Jopson point out, the measurement of sun exposure is complex and the discrepancies above could be sorted out by conducting new studies using compatible protocols in different populations with different levels of sun exposure.

A clearer explanation for the rise in melanoma incidence that takes into account the different effects of chronic and intermittent sun exposure, proposed by Gallagher et al. (15), is that as people have replaced outdoor occupations with indoor, they have engaged in more intermittent sun exposure. Gallagher showed that the decrease in outdoor exposure, or chronic exposure which has an inverse association with melanoma, could explain the increase in melanoma incidence in Canada.

4.2. Artificial Light

Several forms of artificial light have been associated with the development of melanoma in some studies: fluorescent lighting and suntan beds and parlors. Although exposure to fluorescent lighting was hypothesized to increase risk for developing melanoma, there have been no studies to support this idea. On the other hand, the use of tanning lamps and tanning parlors may increase risk for melanoma. The most recently published meta-analysis of the role of sunlamp and/or sunbed use was conducted by Gallagher et al. (16). They evaluated this behavior in a number of ways: ever versus never exposed, first age at exposure and duration of exposure, among them. Although they acknowledged issues of uncontrollable confounding, they conclude that “any exposure to artificial tanning moderately but significantly increases the risk of melanoma.” These authors caution the reader that these conclusions could be modified by the presence of unpublished or unanalyzed data.

4.3. Other Environmental Factors - Arsenic exposure.

The only other environmental factor that has received attention recently is that of arsenic exposure. Freeman et al. (17) recently reported an association of arsenic in toenails – an integrated indicator of arsenic exposure from multiple sources – with the development of melanoma. In 368 cases of melanoma in Iowa, exposure to arsenic increased risk for melanoma by two-fold. In addition, a significant dose response was noted. Interactions with prior non-melanoma skin cancer were observed. Thus, a new potentially important risk factor may be present.

5. HOST FACTORS

Host factors are at least, if not more, important that environmental factors in the development of melanoma. Individuals with darkly pigmented skin are at very low risk for developing melanoma, although they too can do so.

5.1. Phenotypic Factors – Skin Type

 Phenotype in this instance refers to the observable factors, such as skin color, eye color, hair color, freckling, and nevi. Skin color is particularly difficult to quantify and so most studies have evaluated self-reported “skin type”.

The pattern of sun exposure that appears to induce melanoma development is complex and is clearly different by skin type (i.e. propensity to burn, ability to tan). Armstrong and Kricker (18) have proposed a model consistent with data from other epidemiologic studies (19-22) where risk for melanoma increases with increasing sun exposure among those who tan easily, but only with a small amount after which risk decreases with increasing exposure. Among subjects who are intermediate in their ability to tan, risk continues to increase slowly and then at some point declines with increasing exposure. On the other hand, those subjects who have great difficulty tanning have an almost linear increase in risk with increasing sun exposure. This model recognizes that individuals are differentially susceptible to sun exposure and have different levels of risk based on skin type. Moreover, it suggests that different types or patterns of sun exposure are associated with different levels of risk for melanoma.

All studies of melanoma do not support the idea that the effect of the patterns differs among individuals, because most studies of sun exposure and the development of melanoma have collected data using different questions and analyzed them differently, so it is difficult to obtain consistency of effects. One study that illustrates this distinction quite clearly was a cohort study assessing swimsuit use outdoors during adolescence (ages 15-20) in relation to the risk of melanoma (21). In this study Weinstock and colleagues found that swimsuit wearing among sun resistant phenotypes was statistically significantly protective for the risk of developing melanoma (RR = 0.3, 95% CI = 0.1 – 0.8) whereas among sun sensitive phenotypes risk was statistically significantly elevated (RR = 3.5, 95% CI = 1.3 – 9.3). These data in women are consistent with data reported by Holly et al. (22) showing that women who maintain a tan year-round are at reduced risk for developing melanoma (OR = 0.5, 95% CI = 0.3 – 0.9). It is likely that sun-sensitive women are not in this category, as they are unlikely to be able to maintain a year-round tan. A striking example of the critical importance of skin type in relationship to sun exposure as a risk factor for melanoma is seen in the recent study from Spain (23) where without adjusting for skin type farmers were at a significantly increased risk for developing melanoma (OR = 3.3, 95% CI = 1.4-7.8). When adjusted for skin type and age, farmers were at a significantly reduced risk for developing melanoma (OR = 0.5, 95% CI = 0.3-0.8).
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5.2. Nevi

Nevi are the strongest and most reproducible risk factor for cutaneous malignant melanoma. Multiple studies have been conducted that identify nevus count as an important risk factor. There is controversy as to whether atypical nevi are more important than banal nevi in determining risk. This question is very important as atypical nevi have been imputed as intermediate biomarkers in the development of melanoma (24). Some studies find that atypical nevi increase risk rather significantly—from an odds ratio of 4.2 to 51. However, in order to study atypical nevi it is far simpler to use a hospital-based study and so those studies reporting odds ratios of atypical nevi are all hospital based (25-32). A major achievement has been the population-based study conducted in New Hampshire (33). In this study it is clear that atypical nevi do not increase risk more than multiple nevi, as first suggested by Roush et al. (25). A recent meta-analysis by Gandini et al (34) has also demonstrated that multiple nevi and atypical nevi have similar risks.

It is worthwhile looking at the estimates of effect of sun exposure on the development of melanoma in tandem with the other major risk factors for the development of melanoma—nevus number and pigmented phenotype. Work is ongoing to determine the interrelationship of genetic susceptibility and these phenotypic characteristics (35). In data from our large population-based study in Connecticut (36), we estimated the risk for developing melanoma for nevus number, pigmented phenotype, and sun exposure in early life as well as sun exposure 10 years prior to the diagnosis of melanoma, adjusting for age and sex. The risk for melanoma with numerous nevi in this study is 6 times that of someone with few nevi. The risk for melanoma with the most sensitive pigmented phenotype is almost 6 times that of someone with the least sensitive phenotype. However, the risk for melanoma with increasing early life sun exposure or increasing later life sun exposure is only 2 times that of someone with the least sun exposure. Clearly, genetically determined characteristics such as nevi and pigmented phenotype are more powerful determinants of melanoma risk than is sun exposure.

5.3. Reproductive Factors

Concern regarding the possible association between pregnancy and development of malignant melanoma arose from early case reports of aggressive disease that was observed in pregnant women (37-39). Such concern persists despite contrary evidence that emerged in intervening decades [40-41]. A major rationale underlying this concern is the hyper pigmentation that often occurs in pregnancy. Many women experience a darkening of the skin on the face, abdomen, and other areas of the body during pregnancy, a condition known as melasma [42]. Melasma has also been associated with use of exogenous hormones [43-44]. Such evidence that melanocytes may be stimulated by hormones has fueled speculation that pregnancy-associated hormones could also influence the risk of melanoma.

Results from relatively recent studies based on relatively large numbers of cases, augmented with information on prognostic factors, suggest that pregnancy does not influence prognosis of melanoma although earlier reports had suggested they did. These studies had well-defined case and control groups and ascertained relevant information about multiple prognostic factors for melanoma. In each of these studies, there was no significant difference in overall survival between melanoma cases diagnosed during pregnancy and their respective control groups (45-52). In four of these studies (45, 47-49), women who developed melanoma during pregnancy had thicker tumors than the controls and were more likely to develop recurrent disease. Nonetheless, overall survival did not significantly vary among cases and controls in these studies.

Reported associations between exogenous hormone use and melanoma. Reports from three cohort studies conducted in the 1970’s documented an increased risk for melanoma among women exposed to exogenous hormones (53-55). However, an overwhelming majority of studies conducted since that time reported equivocal findings – no association- or risks that were restricted to defined sub-groups (56-57).

Consistent evidence of an association between estrogens and melanoma has not emerged. Prentice and Thomas (56) systematically reviewed results from case-control and cohort studies that were conducted in the 1970’s and 1980’s to examine the association between use of oral contraceptives and melanoma. Results from most case-control studies showed no overall association between use of oral contraceptives and melanoma (58-64), though one study showed a modest positive association that did not achieve statistical significance (53).

The bulk of evidence amassed over the past half century suggests that pregnancy does not significantly affect the risk of developing malignant melanoma. Further, pregnancy does not appear to adversely influence survival from the disease. Results from some studies suggested that pregnant women with melanoma were more likely than their non-pregnant counterparts to exhibit adverse prognostic indicators, specifically, thicker lesions and shorter time to recurrence. Nonetheless, most studies found no difference in overall survival between pregnant and non-pregnant women with melanoma. Recent reports from large-scale, population-based studies support these conclusions.

6. GENETIC SUSCEPTIBILITY

Genetic studies have consistently suggested that the genetic etiology of melanoma is highly complex. Linkage analyses have suggested that several genes (including genes on chromosomes 1 and 9) may account for melanoma among families with multiple cases (65-67).

An early linkage analysis conducted by Cannon-Albright (68) found a dominant, partially-penetrant melanoma susceptibility locus on the short arm of chromosome 9. Penetrance of this gene among the 11 families studied was estimated to be 53% by the age of 80.
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In addition, gene carriers had higher nevus counts than non-carriers. Kamb subsequently identified the gene as CDKN2A, at 9p21 (69). This tumor suppressor gene codes for a low-molecular weight cell cycle control protein, p16\(^{Ntks}\), that inhibits excessive cell proliferation by inhibiting the activity of the cyclin D1-cyclin dependent kinase 4 or 6 complex (70).

Bishop et al. (71) evaluated the penetrance of this gene in an international family study of melanoma and estimated it to be 91% over a lifetime in high sunlight areas such as Australia. However, Begg et al. (72) in a population-based analysis of penetrance, found that actually the penetrance was far lower and ranged from 14% at age 50, 24% at age 70 and 28% at age 80. Clearly, it is important to specify the population sampled carefully. In the GEM study, reported by Begg, population-based samples from registries were used to identify the penetrance whereas the Bishop paper is reporting on families who were actually identified because they have multiple cases. Probably, there are additional important but as yet unknown risk factors for melanoma that may account for the differences. An important result of this study is that genetic testing of families with a history of melanoma would be likely to identify few mutations in CDKN2A. This is a critical point for genetic counselors and cannot be overemphasized.

Studies have evaluated gene-environment interactions. Goldstein, for example, examined the relationship between CDKN2A mutations and dysplastic nevi, total nevi and solar damage (73). She evaluated data on 20 American melanoma-prone families, 13 of whom had co-segregating CDKN2A mutations. There was evidence of a gene-covariate interaction between dysplastic nevi and total nevi but not with solar damage.

A second melanoma susceptibility locus, CDK4 was identified on the long arm of chromosome 12, but it has only been found in 3 families to date (74). This gene’s function is to bind to the cell-cycle control protein p16.

A third susceptibility locus has been narrowed to 1p22 (68). However, the gene has not yet been identified.

Finally, recent studies have suggested that specific genetic polymorphisms may be associated with the risk of melanoma (75). The melanocortin receptor gene (MC1R) is a major pigmentation gene and multiple studies have associated this gene with red hair. In fact, a constellation of 3 and sometimes 5 variants in this gene are called the “red hair variants”. Independent associations of MC1R with the development of melanoma have also been reported.

Other genes, such as DNA repair genes, metabolizing genes and those associated with the vitamin D synthesis pathway, have been associated with melanoma; however, there has not been sufficient study of these to determine how robust the associations are. Many studies are ongoing at this time to look at these low penetrant genetic variants and their associations with melanoma risk.

7. CONCLUSION

In conclusion, although melanoma has been intensively studied by epidemiologists for at least 50 years, there are many new twists in the understanding of risk, and these—particularly the role of genetic factors in relationship to environmental factors—will be evaluated in future editions and in new studies.

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Epidemiology of cutaneous melanoma


Epidemiology of cutaneous melanoma


Epidemiology of cutaneous melanoma

Key Words: Melanoma incidence, Melanoma Mortality, Ultraviolet Radiation, Sun Tan Parlors, Genetic Epidemiology, Review

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