

Epidemiology of Melanoma

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Malignant melanoma represents a significant and growing public health burden in the US and worldwide. It is estimated that 68,130 cases of invasive malignant melanoma and at least 48,000 cases of melanoma in-situ will be diagnosed in the US this year. Melanoma is also one of the few remaining cancers with increasing US incidence. In the 1930s, the lifetime risk of an American developing invasive malignant melanoma was 1 in 1,500. Currently, that risk is 1 in 59. Deaths from malignant melanoma are also increasing. The mortality rate from malignant melanoma has risen about 2% annually since 1960. This year, it is estimated that 8,700 Americans will die from this cancer. The identification of individuals at high risk for malignant melanoma is important for the development of focused and efficient prevention efforts. Acute sun exposure resulting in sunburn remains a significant risk factor for the development of melanoma, but numerous other potential risk factors have been cited. Included among these are atypical mole syndrome/dysplastic nevus syndrome, blistering sunburns, immunosuppression, prior therapy with psoralen with ultraviolet A light (UVA) light, UV exposure at tanning salons, elevated socioeconomic status, and history of melanoma in a first-degree relative. With a better understanding of the reasons for the increasing rate of this cancer, and with enhanced early detection approaches, we may be able to decrease the incidence and mortality of malignant melanoma.

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Melanoma is an increasingly important public health problem in the United States and worldwide. The incidence of melanoma has been increasing faster than that of any other cancer in the United States.¹ Overall, melanoma incidence increased 3.1% ($P < 0.001$) annually during the last 20 years. More than 68,130 new cases of invasive melanoma are expected to be newly diagnosed in 2010.² Statistically significant increases are occurring for tumors of all histologic subtypes and thicknesses, including those greater than 4 mm.

At current rates, the lifetime risk of an American developing invasive Melanoma is 1 in 59³ (Fig. 1) overall and 1 in 39 for white men and 1 in 58 in white women. This finding contrasts dramatically with a lifetime risk of 1 in 1500 for Americans born in 1935.⁴ It has been estimated by U.S. Surveillance, Epidemiology and End Results Program (SEER) that there are approximately 793,283 men and women alive in the United States who had a history of invasive melanoma (385,054 men and 408,229 women).⁵

Fortunately, there has been steady improvement in melanoma survival over decades with the 5-year survival for in-

vasive melanoma increasing from 82% in 1979 to 92% in 2002.⁶ Because the primary treatment modality of cutaneous melanoma, surgical excision, has not changed substantially during the past several decades, the improved 5-year survival rate can be primarily attributed to earlier detection. Earlier detection and therapy also leads to decreased cost of therapy. An estimated 90% of costs spent on melanoma therapy in the United States are related to those with advanced disease.⁷ Therefore, a significant savings in health care cost can be realized if melanoma incidence could be lowered or if it could be detected in an earlier, more easily treated phase.

However, skin cancer is one of the few cancers in which the cause of most cases is known—excessive sun exposure,⁸ and it would be expected that lowering an individual's ultraviolet (UV) exposure should similarly improve later risk of developing skin cancer. However, other factors influence the risk of developing and dying from this cancer.

Incidence

Melanoma incidence has increased exponentially in the United States since the 1930s. The earliest measure of melanoma incidence in the United States was in Connecticut during 1935 to 1939 at 1.0 per 100,000.⁹ In 1973, the U.S. melanoma incidence rate was 6.8 per 100,000 and by 2003 to 2007, this rate had climbed to 20.1 per 100,000. The

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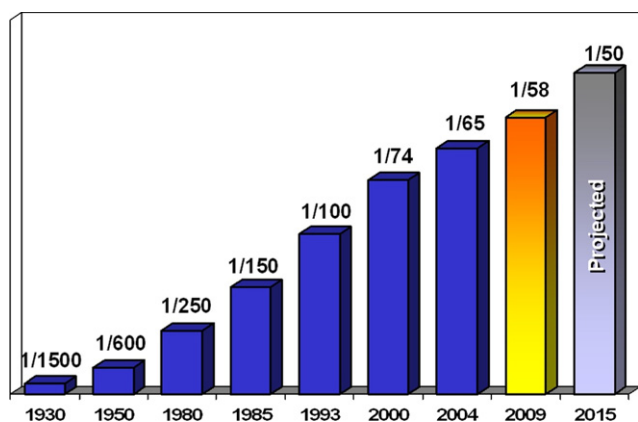


Figure 1 U.S. invasive melanoma lifetime risk.⁴

increase in invasive melanoma incidence was 4.6% per year from 1975 to 1985 and 2.6% per year from 1996 to 2007 (Fig. 2).¹⁰ On the basis of rates from 2005 to 2007, 1.93% of men and women born today will be diagnosed with melanoma of the skin at some time during their lifetime.

Melanoma is currently the fifth most common cancer diagnosed in men, with 38,870 cases expected this year (5% of all cancers diagnosed). In women melanoma this year will be the seventh most common cancer in the United States with 29,260 cases (4%).¹¹

Gender differences are noted in melanoma incidence. In the United States, melanoma is more common in men than in women. In 1973, the incidence rates were 7.3 per 100,000 in men and 6.4 per 100,000 in women. In the 2003 to 2007 period, the incidence rate increased in men to 25.6 per 100,000 and 16.2 per 100,000 in women.¹²

The incidence of melanoma is greater in women than men until they reach the age of 40 years. However, by 75 years of age, the incidence is almost 3 times as high in men versus women (145.6 vs. 47.3 per 100,000).¹⁰ In the United States, more recent generations of men have similar incidence rates compared with previous generations, even though incidence rates are still increasing in older generations of men.¹³ However, incidence appears to be increasing in more recent generations of women, possibly because of an increased usage of tanning beds by this group.

Ethnicity may also relate to incidence trends. The incidence of melanoma is significantly lower in nonwhite populations. A recent study comparing Hispanic and non-Hispanic males in California showed that the incidence rates were increasing more rapidly and more advanced tumors were diagnosed in the Hispanic population.¹⁴ In 2007, SEER data showed an incidence rate in the United States in whites of 27.5 and in blacks of 1.1 per 100,000.¹⁵

Mortality

From 2003 to 2007, the median age at death for melanoma of the skin was 68 years of age. Approximately 0.1% of those younger than 20 years of age died; 2.7% between 20 and 34 years; 6.3% between 35 and 44 years; 14.3% between 45 and

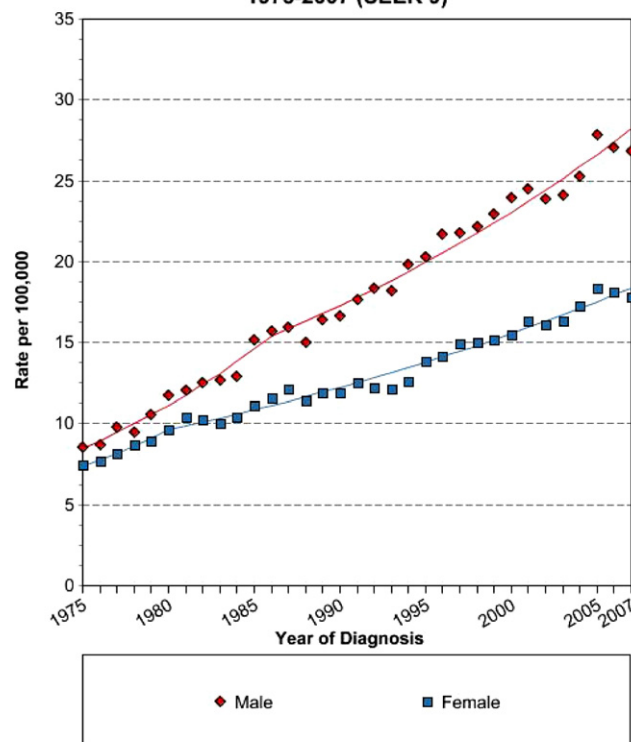
54 years; 19.6% between 55 and 64 years; 20.9% between 65 and 74 years; 24.1% between 75 and 84 years; and 11.9% 85+ years of age. For this period, the age-adjusted death rate was 2.7 per 100,000 men and women per year.¹⁶ More than 75% of skin cancer deaths in the United States are attributable to melanoma.¹⁷ It is estimated that in 2010, 8700 Americans will die of this cancer.¹⁸

Melanoma mortality has consistently increased in the United States during the last 30 years, although the increase appears to be flattening. Mortality increased 1.6% annually in U.S. population between 1975 and 1989 but has been flat from 1990 to 2007.¹⁹ There is a greater mortality rate in men compared with women of the same age in the United States. In men, there was a significant increase in annual percent change in melanoma mortality of 2.3% from 1975 to 1989 and 0.2% from during 1989 to 2007. In women, the annual percent change in melanoma mortality was 0.8% between 1975 and 1989; however, in recent years (1989-2007) it appears to be decreasing at the rate of -0.6%.

Risk Factors

Risk factors for melanoma (Table 1) include natural UV exposure, indoor tanning, family history, nevi, and several other factors, all of which are discussed in this section.

Age-Adjusted Delay-Adjusted SEER Incidence Rates
By Sex
Melanoma of the Skin, All Ages, All Races,
1975-2007 (SEER 9)



Cancer sites include invasive cases only unless otherwise noted. Delay-Adjusted Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii Iowa, New Mexico, Seattle, Utah, and Atlanta). Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.4.3, April 2010, National Cancer Institute.

Figure 2 U.S. melanoma incidence by gender 1975-2007.¹²

Table 1 Risk Factors for Melanoma

Risk Factor	Impact
Sun (UV) exposure	
Cumulative	May influence risk in the head/neck region
Sporadic	Intense, intermittent exposure and blistering sunburns in childhood and adolescence are associated with increased risk
Artificial UV exposure (tanning)	Indoor tanning bed exposure significantly increases risk. The use of psoralen UV therapy may increase risk
Family history	Occurrence of melanoma in a first- or second-degree relative confers increased risk. Familial atypical mole melanoma syndrome within a context of a history of melanoma confers an even higher risk
Dysplastic nevi	Markers for increased risk. Increasing impact with family history.
Other nevi	A large number of melanocytic nevi and giant pigmented congenital nevi confer increased risk
Age	Age-related incidence rises with increasing age
Gender	Greater overall in men. Greater in women until age 40 then 2:1 males/females by age 80.
Skin type/ethnicity	Increased incidence in those with fair complexions and red headed, those who burn easily, tan poorly, and freckle
Occupation	Greater incidence in indoor workers, as well as those with higher education and income, pilots and firefighters
Socioeconomic status	Increased with higher incomes
Ionizing radiation	Possible association
Chemicals and pollutants	Possible association with arsenic exposure
Diet and nutrients	Elevated body mass index may increase risk

Natural UV (Sunlight) Exposure

The skin is the most exposed organ to environmental UV and to its related effects.²⁰ The p53 suppressor gene, which is often found to be mutated in melanoma, is directly affected by UV exposure.²¹ The primary wavelengths influencing melanoma risk are most likely in the UVB (290–320 nm) range. However, animal studies have also demonstrated a small effect on melanoma development as the result of exposure to UVA wavelengths.^{22,23} Persons with type I and II skin types who are more sensitive to the effects of exposure at these wavelengths are at higher risk for the development of skin cancer.²⁴

The amount of average annual UV radiation correlates with the incidence of melanoma.²⁵ The closer an individual is to the equator, the greater the intensity of UV exposure that occurs. U.S. SEER incidence shows a direct relationship between the incidence of melanoma and latitude.

The correlation of melanoma incidence to UV radiation exposure is greater when ambient UVA (320–400 nm) radiation is also included.²⁶ Individuals in high-altitude regions tend to have a greater melanoma rate that may be related to the greater UV fluences (J/cm²) noted at these sites.²⁷ Melanoma risk has also been noted to be directly related to annual UV exposure. When lifetime residential history was coupled with levels of midrange UV radiation (UVB flux) to provide a measure of individual exposure to sunlight a 10% increase in annual UVB flux was associated with a 19% increased risk of melanoma.²⁸ Even in women who could develop a deep tan, a 10% increase in hours outdoors was associated with 5.8% increase in the incidence of melanoma. Melanoma mortality rates have also been shown to directly correlate with ambient UV exposure.²⁹

The anatomic areas that melanoma develops on appear to be somewhat related to the average amount of UV ex-

posure to those sites.³⁰ Melanoma tends to be found more frequently on the legs in women, where more episodic UV exposure may occur than in men and more commonly on the back in men in whom a similar UV exposure history is found.³¹

The point in life when UV exposure occurs is important in its effect on subsequent skin cancer risk. Acute intermittent UV exposure elevates the risk of developing melanoma in the future.³² The authors of migration studies have demonstrated sun exposure early in life may have a greater influence on subsequent skin cancer risk than does that at a later age. Persons born in the high UV radiation environment of Australia have an increased risk for developing melanoma compared with those born in Northern Europe who migrated at age 10 or older.³³

However, more recently a study has found that excessive UV exposure later in life may be equally important to that occurring earlier. Pfahlberg et al³⁴ found an increasing gradient of melanoma risk in exposure categories related to the frequency of sunburns comparing UV exposure occurring before and after age 15. More than 5 sunburns doubled the melanoma risk, irrespective of their timing in life suggesting that the hazardous impact of UV exposure seems to persist throughout life.

Studies have shown that a simple behavioral change, protection from UV exposure, can lower subsequent melanoma risk.³⁵ Therefore, protection from both UVB and UVA needs to be achieved. Broad-spectrum sunscreens provide better protection from UV induced neoplasia.³⁶ Seite et al have demonstrated that daily use of broad-spectrum photoprotection can significantly reduce UV induced skin damage and subsequent skin cancer risk.³⁷

Indoor Tanning

Nearly 30 million people tan indoors in the United States annually, including 2.3 million adolescents. Despite increased evidence on the dangers of artificial UV radiation, the popularity of indoor tanning is growing.³⁸ The relationship between UV exposure from tanning beds and subsequent development of melanoma has now been well documented.

More than 20 case control studies have investigated a possible link between indoor tanning and melanoma.³⁹ The more recent, more rigorously designed studies have found a positive correlation with increased melanoma risk. A study of 571 first-time melanoma patients compared with 913 healthy controls found a significantly elevated odds ratio of 1.8 between indoor tanning and melanoma.^{23,40} In another study of 1518 dermatology patients surveyed for skin cancer history and tanning bed use, a significant increased risk of malignant melanoma was noted for ever use of indoor tanning (odds ratio 1.64), and a very strong correlation was noted for women aged 45 years or younger who used indoor tanning equipment (odds ratio 3.2).⁴¹ Persons with tanning bed usage history with a history of melanoma are also at increased risk for additional subsequent primaries.

A meta-analysis of 19 studies of indoor tanning and melanoma risk suggested ever use of indoor tanning was associated with the development of melanoma with a relative risk of 1.15, whereas first use before the age of 35 years showed a significantly increased risk of melanoma, with a summary relative risk of 1.75.⁴² On the basis of this study and others, the International Agency for Research on Cancer classified UV exposure from tanning beds at its highest carcinogenic risk category ("carcinogenic to humans").⁴³ The National Institutes of Health has also concluded that "exposure to sunbeds and sunlamps is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in human, which indicate a causal relationship between exposure to sunbeds and sunlamps and cancer." Indoor tanning has also been calculated to be directly associated with melanoma deaths.⁴⁴

Previous and Family History

To date, the exact genes that increase melanoma risk have not been fully described. However, there is a clear relationship between a previous or family history and melanoma risk. A personal previous history of melanoma increases risk for a second primary by a factor of 8-10x.⁴⁵ Approximately 10% of melanomas present in familial clusters.⁴⁶

Two high-penetrance genes definitively associated with hereditary melanoma, cyclin-dependent kinase inhibitor 2 A (*CDKN2A*) on chromosome 19p21 and cyclin-dependent kinase 4 (*CDK4*) on chromosome 12q14 have been identified.⁴⁷ Mutations in *CDKN2A* account for approximately 20% to 40% of hereditary melanoma, and 0.2% to 1% of all melanomas.⁴⁸ Mutations in *CDK4* are rare and have been reported in fewer than 15 families worldwide, leaving *CDKN2A* as the most significant melanoma predisposition gene identified thus far.

Nevi

The number of nevi that a person has is directly related to melanoma risk. Dysplastic nevi are a relatively common clinical entity found in 2% to 6% of the U.S. population.⁴⁹ The clinical relevance of these lesions lies in their well-recognized contribution to an increased risk for melanoma. Studies have demonstrated that dysplastic nevi are reported in up to 34% to 56% of melanoma cases,⁵⁰ and their presence may confer up to a 10-fold increase in melanoma risk.⁵¹

The development of potential precursors to melanoma, such as dysplastic nevi, has been shown to be inhibited by the regular use of sunscreen.⁵²⁻⁵⁴ Personal nevus count has been shown to be related to the risk of developing melanoma.⁵⁵ Lower nevus counts were found in children who regularly used sunscreens than those who did not, suggesting that sun protection early in life might lower subsequent melanoma risk.⁵⁶

Other Factors

The risk of melanoma increases with age and the risk is greater in males. An inability to tan is associated with increased melanoma risk. Despite the identification of more than 100 loci involved in vertebrate pigmentation, the *MC1R* gene is consistently a major determinant of pigment. The human *MC1R* coding region is highly polymorphic, with at least 30 allelic variants, most of which are associated with red hair. The "red-head" phenotype is defined not only by hair color but also by fair skin, inability to tan, a propensity to freckle, and high levels of pheomelanin.⁵⁷

A number of investigators have reported that melanomas are more prevalent in the wealthier socioeconomic levels. Studies have shown that the incidence of melanoma in age-matched sections of the population is greater in those with a larger income and other measures of affluence.⁵⁸ This may be attributable to the greater opportunity of the more affluent for recreational sun exposure and sunny holidays in the winter months. However, melanoma mortality is lower in the more-affluent groups.⁵⁹ This finding may be related to better access to care. Certain occupations are associated with increased melanoma risk. Firefighters,⁶⁰ pilots, and finance professionals⁶¹ are consistently found in studies to be at the greatest risk for melanoma.

Immunosuppression increases melanoma risk. Organ-transplant patients have an 8-fold increased chance of developing melanoma.⁶² Several studies have suggested that a greater body mass index may be associated with an increased risk of melanoma.⁶³

Conclusions

Melanoma remains a significant public health problem in the United States. The incidence continues to increase at high rate and deaths from melanoma are also increasing. The endogenous risk factors that we currently recognize are often surrogates for genetic markers yet to be determined. Exogenous risk factors need to be better defined and understood to help to develop better public education programs that can

change risk behaviors and subsequently lower future incidence and mortality from melanoma.

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