

THE MELANOMA EPIDEMIC: *RES IPSA LOQUITUR*

Abstract

Many have debated whether or not we are in the midst of a melanoma epidemic. Some facts are clear and helpful to this debate, while others are less clear. The incidence and mortality of melanoma have increased over several decades, but the incidence has risen faster than the mortality. The incidence has risen three to seven percent on average over several decades and even more rapidly among Caucasian men and the elderly. In the U.S., the incidence in men is higher than women after the age of 40, and the difference between men and women increases from age forty until the end of life. The incidence in the U.S. has risen most rapidly among in situ and localized lesions, but distant and regional disease has increased as well. Among localized disease in the U.S. from 1988-1997, all stages increased by comparable amounts. This strongly argues against the idea that the increase in incidence of melanoma is *only* due to early detection of thin lesions or biologically benign lesions, at least during the time period studied. On the other hand, early detection of thin lesions may well account for lower increases in mortality than incidence and improvements in survival. Survival has increased from approximately 60% in the 1960's to 89% in recent years. Improvements in survival appear to be related to earlier diagnosis, rather than improvements in survival of a given stage.

Studies consistently point to a major role of ultraviolet light exposure as the most important risk factor for those individuals with a phenotypic susceptibility. Public health efforts aim at primary and secondary prevention strategies. Primary prevention strategies attempt to prevent one from developing melanoma, primarily through avoiding exposure to ultraviolet light. There is particular emphasis on avoidance of ultraviolet exposure in childhood and young adulthood, when it appears the risk is greatest. When strict avoidance cannot be adhered to, sunscreens have been logically recommended. Secondary prevention strategies include screening campaigns and educational campaigns. Many of these strategies appear promising but require further rigorous testing. The melanoma epidemic has arisen for a variety of reasons including: a true increase in melanomas of malignant behavior, a particularly high increase in localized and in situ lesions, and an increase in the number of biopsies performed that may have resulted in the increased detection of less aggressive lesions. The contribution of possible changes in the diagnostic criteria for melanoma to the increased incidence remains unknown.

Introduction

Much ado has been made about whether the melanoma epidemic is a real or artificial phenomenon. In this debate as in most, *res ipsa loquitur* applies...”the thing speaks for itself” or colloquially “let the facts speak for themselves”. Melanoma incidence and mortality have risen dramatically during this century in almost all countries and in fair-skinned populations in particular. In the U.S. in 1935, one’s estimated lifetime risk of

disease was 1 in 1500. In the U.S. in the year 2000, the lifetime risk of melanoma was estimated at 1 in 75 persons. In Australia, the lifetime risk has been estimated at 1 in 25¹. These stark numbers have placed melanoma in the category of an “epidemic.” The exact nature of this epidemic has been debated. Some have questioned whether the epidemic is a true public health concern, or is in fact a sign of increased efforts at screening and diagnosing the disease^{2,3}. Others do not hold this view⁴. Some have suggested much of the increase has been in a non-metastasizing biologically benign form of melanoma or simply in changes in the diagnostic criteria for melanoma by histopathologists^{2,3}. The implications of whether the epidemic should be a true public health concern, are substantial. In many countries worldwide melanoma is of significant concern and in these countries public interventions are being conducted to promote earlier detection and treatment of the disease. Are these efforts worthwhile or would resources be better spent elsewhere? The answer depends not only on the interventions themselves, but also on whether the epidemic is “real”. The most recent data on the melanoma epidemic suggests that while melanoma is being diagnosed earlier accounting for much of the increase in incidence, the percent increase of localized tumors of all Breslow levels have increased since the late 1980’s (see Chapter Three). Moreover, mortality has been increasing at rates that warrant concern. In this paper, I will review the incidence, mortality, and survival data on melanoma from the U.S. and other countries in an attempt to gain insight into the melanoma epidemic. I will also review studies on the etiology of melanoma and preventative efforts being undertaken.

Incidence

The annual incidence of melanoma among Caucasians has risen rapidly¹, between three and seven percent over the last several decades⁵⁻⁷. According to the most recent statistics in the U.S., the incidence has not abated though a recent Joinpoint analysis of Surveillance, Epidemiology, and End Results (SEER)⁸ data showed the incidence rose less sharply in the most recent years⁶. The incidence of melanoma in the U.S., in 1997 was 14.3 per 100,000⁸. This is a sharp increase from 5.7 per 100,000 in 1973. The incidence is not uniformly distributed over the population. Caucasians, the elderly, and men seem to have the highest rates. In the U.S., men have higher rates than women, whereas in countries with lower incidence rates, women generally have higher rates than men. For men, the U.S. 1973 and 1997 incidence rates are 6.1 and 17.2 per 100,000. For women, the comparable 1973 and 1997 statistics are 5.4 and 12.0 per 100,000. Not only are elderly men at higher risk than elderly women, but the rate of increase in recent years among elderly men also has been higher than in elderly women. Caucasians are much more at risk with Hispanics, Asians, and African-Americans who had rates of 2.9, 1.1, and .8 per 100,000 from 1990-1997 (SEER). In Australia, the incidence of melanoma is the highest in the world at more than 40 per 100,000 persons whereas in certain Northern European countries the incidence is less than 5 per 100,000 persons⁹. Persons with fairer skin types, who move closer to the equator, increase their risk of melanoma¹⁰.

Birth cohort also influences one's risk of melanoma with later birth years being associated with higher age-specific incidence rates and with differences between

¹ Reference 7 and my analyses on incidence referenced in this chapter are presented in Chapter Three.

successive birth cohorts increasing more rapidly over time⁷. There has however, been a leveling off of the rate of rise in incidence in birth cohorts since the 1960's in Australia^{1,11} and the U.S.⁴. The causes of this slowdown in the rate of rise in incidence for these latter cohorts are unknown but could relate to primary prevention effects.

Melanoma incidence is also dependent on age and gender^{6,7}. Incidence rises with age, especially in men. In the U.S., women have a slightly higher risk of melanoma than men before age 40. After 40, men have a higher incidence and the difference becomes remarkably large with increasing age. By age 85, the incidence in men is approximately twice that in women.

Recent results suggest significant increases in early stage melanomas and in situ lesions^{4,12}. Some have questioned whether this increase is primarily due to early detection or to detection of clinically insignificant lesions^{2,3}, but further empirical analysis is needed. In a recent analysis of SEER data we found that melanomas of all stages increased from 1988 to 1997, but localized lesions and in situ lesions increased the most⁷. However, among localized lesions there was an increase in melanomas of all Breslow thickness levels, which are the best predictors of prognosis independently and in multivariate analyses. In absolute numbers, thin lesions accounted for the majority of the increase. Yet, lesions of greater Breslow levels, though smaller in number, increased at comparable rates to thinner lesions. This strongly argues against the idea that the increase in incidence of melanoma is only due to early detection of thin lesions, at least during the time period studied, 1988-97. If early detection of thin lesions alone

were the case, one would expect for a time to see an increase in the incidence rates of thin melanomas followed by a decrease in the incidence rates of thin lesions. In that scenario, the apparent increase in incidence followed by a decline is attributable to the fact that first screenings detect the prevalent lesions and subsequent screenings detect only the cumulative incident cases since the last screening. However, in such a scenario, one would also expect a decrease in the incidence rate of thick lesions shortly after the increase in thin melanomas, *ceteris paribus*. This would happen because there would be less thin lesions to progress to thick lesions. These findings typical of early detection campaigns and screening were not detected in our analysis however, and this suggests increased screening is not the major factor responsible for the increase in melanoma incidence during the time period studied.

Mortality and Survival

Two key factors are important regarding melanoma mortality rates. First, mortality rates have risen over the last three decades⁸. Second, they have not been rising nearly as fast as incidence rates⁸. Why are these two facts important? If the melanoma epidemic were due to biologically benign lesions *alone*, we would expect no increase in mortality, *ceteris paribus*. On the other hand, if one assumes that the treatment has not changed stage-specific mortality dramatically, the fact that mortality rates have not risen as fast as incidence rates suggests a change in the stage distribution of disease. This implies that relatively more of the increase in incidence is due to the detection of lesions, which are less lethal or less aggressive than is due to biologically aggressive lesions.

Mortality rates among fair-skinned people range from one to three per 100,000 people per year in the Northern hemisphere. In Australia and New Zealand the rates are even higher in the five to ten per 100,000 people range. Rates have not been changing equally among all strata of the population. While mortality rates in the US have risen among older cohorts, younger cohorts have seen steady or declining mortality rates in recent years. Furthermore, on subgroup analysis from 1992-98 the mortality rates among males increased while the rate for females actually declined. The mortality rate in whites also increased more than in non-whites. Mortality rates, like incidence rates also show age-specific trends. Older cohorts continue to show increased mortality in almost all countries, while younger cohorts show no increase or falling rates^{9,11}. These trends are not succinctly explained by patterns of sun exposure alone.

While mortality rates have increased, survival for those diagnosed with melanoma has also increased in the U.S., Europe, and Australia. For instance, the survival rates in whites from 1960-63 were estimated at 60%, the survival from 1974-76 was 80%, and the survival from 1992-97 was 89%⁸. The reasons for this are not quite clear though it likely has to do with earlier diagnosis at a more favorable stage rather than improved survival of late stage disease. These countries with improved survival also have made educational campaigns a priority though no clear causal link to improved survival from these plans has been documented.

Stage Distribution of Disease

Most melanomas are localized and the trend is for the percentage of localized disease to continue rising⁷. From 1992-1998 the stage distribution of U.S. melanoma cases in SEER were as follows: Localized disease 82%, regional disease 9%, distant disease 4% (6% were unstaged). From 1988-97, young patients and women had a higher incidence of melanomas of thinner Breslow levels when compared to older patients or men. Older patients and men had a higher incidence of melanomas of thicker Breslow levels compared to younger patients or women. For instance, in women under forty, the incidence of melanomas of Breslow level 1 is nearly twice that of men. On the other hand, for men over age sixty, the incidence of melanomas of Breslow level 4 is over twice that of women. From 1988 to 1997, the incidence of in situ lesions grew faster than localized disease of Breslow thickness levels 1 to 4, which increased faster than regional disease, which increased faster than distant disease. However, within localized disease, lesions of all Breslow levels increased at fairly comparable rates⁷. Because of a shift in the stage distribution of melanomas towards thinner lesions with a disproportionate increase in incidence relative to mortality, some have questioned whether some of these thin lesions removed would have ever progressed^{2,3,13,14}. The idea they are suggesting is that some of these thin melanomas may be biologically benign and may never have become clinically relevant had they not been biopsied. They are simply being detected now because of the increased propensity for physicians to biopsy pigmented lesions. While this may be true there is no consensus that such biologically benign melanomas exist. Certainly, spontaneously regressing and slow growing, often benign-behaving, and sometimes remitting variants of other cancers are

thought to exist, with actinic keratoses being one example. However, once a lesion is removed, one has lost the ability to follow its natural history. It is likely that the increases in incidence and changes in stage distribution do represent changes in biopsy patterns and diagnostic criteria to some degree. However, in the U.S. increases in the incidence of lesions of higher Breslow levels are not consistent with this “epidemic” solely being due to biologically benign lesions.

Etiology and Risk Factors

What has caused the dramatic increase in the incidence of melanoma over the last several decades? Studies trying to unravel the epidemiological causes of melanoma are difficult at best. Consistently though, studies point to a major role of ultraviolet light exposure as the most important risk factor for those with phenotypic susceptibility. The dramatic increases in melanomas seen over the last decades may be the result of changes in behavioral patterns relating to sun exposure and to a lesser extent ozone depletion¹⁵⁻¹⁷. Studies suggest that a 1% reduction in ozone, may lead to an increased incidence of malignant melanoma of 0.6%¹⁶. The United Nations Environment Program estimated that in the event of 10% decrease in stratospheric ozone, an additional 300,000 cases of non-melanocytic and 4,500 cases on melanoma could be expected worldwide on an annual basis. Studies show that in general melanoma prevalence increases with proximity to the equator controlling for other factors such as skin type. As is almost always the case with cancer, environmental exposure affects people of different predispositions to melanoma differently. In the fair skinned, red-haired, blue-eyed person who burns easily and rarely tans; the exposure to ultraviolet light appears

to have an enormous real impact on melanoma risk. As an example, the risk of melanoma in whites in Australia is much higher than in Great Britain where it is also high, despite a common ancestry and phenotypic characteristics. The main reason for the different rate of melanomas appears to be predominantly the higher ultraviolet light exposure in Australia. A clever study from Australia showed that immigration to Australia before the age of 10 increases one's risk of melanoma to that of a native Australian while immigration after age 15 yields rates one-fourth native Australians¹⁰. The exact manner in which ultraviolet light induces melanoma is not clear. Also, the part of the ultraviolet spectrum responsible for melanoma induction is not certain either.

It is thought that sunburns, especially in early life are the most important risk factor for the development of melanoma. One or more severe sunburns in one's youth, roughly doubles the lifetime risk of melanoma¹⁸. Case-control studies have shown with consistency that intermittent exposure, particularly if sufficient to cause sunburn, is an important factor for developing skin cancer¹⁹⁻²¹. The male ear, which has a large amount of exposure to the sun, also has the highest incidence of melanoma of any body site per unit area²². Also, patients with melanoma have increased solar elastosis, actinic keratoses, and non-melanoma skin cancers, consistent with increased ultraviolet exposure²³. Ultraviolet exposure appears to result in melanoma after a long lag-time of years to decades. One the strongest correlates of melanoma development is from those who recall many childhood burns before the age of twenty. Of course such studies are prone to recall bias, i.e., the patient is more likely to remember he or she had severe sunburns only because they have developed a melanoma and thought

about it sufficiently long. It may not be young age per se that is so important, as much as the behaviors associated with young age, namely sun-exposure and sunburns. Superficial spreading melanoma appears to be the melanoma type most associated with intermittent sunburns. The evidence for total sun exposure as a risk factor is less clear. In fact, work-related exposure may be protective. Lentigo maligna is the skin cancer most associated with total sun exposure and unlike superficial spreading melanoma is a disease almost exclusively of people older than 40, with a dramatic increase in incidence with age. It is also more common in men than women and from age 45 to 85+ the incidence increases approximately 15-fold⁷.

From numerous studies, there appears to be a relationship between ultraviolet light exposure and the development of nevi, which are a key risk factor for the later development of melanoma²⁴⁻²⁷. Complicating this is the fact that skin type is related to both tendency to develop melanoma and nevi. However, even when controlling for skin type, nevi are a central risk factor for the development of melanoma²⁴. Risk factors for melanoma include both clinically and or histologically “atypical moles”, increased numbers of acquired “normal” nevi, the dysplastic nevus syndrome, a family or personal history of melanoma, a personal history of nonmelanoma skin cancer, giant congenital nevi (more than 20 cm), and immunosuppression. The dysplastic nevus syndrome consists of people with at least one or two first- or second-degree relatives with melanoma and numerous nevi, some of which are atypical. People with this syndrome have a relative risk for melanoma from 33 to 1,269, with a cumulative lifetime risk of almost 100 percent^{28,29}.

Public Health Initiatives

Efforts have been underway for years with varying amounts of vigor to fight the increased incidence and mortality from melanoma. Perhaps the mortality has not increased as much as incidence because of such efforts, but research has not yet determined this to be the case. Public health efforts aim at primary and secondary prevention strategies. Primary prevention strategies attempt to prevent one from developing melanoma, mostly through avoiding exposure to the primary risk factor, ultraviolet light. There is particular emphasis on avoidance of ultraviolet exposure in childhood and young adulthood when it appears the risk is greatest. When strict avoidance cannot be adhered to, sunscreens have been logically recommended. Interestingly, high quality evidence to support the use of sunscreens has mostly been lacking. In fact, most reports have found no effect or an increased risk of melanoma with sunscreen use. As untenable as this seems, it deserves further evaluation, given the findings. It must be emphasized however that these studies showing increased risk are by and large non-randomized case series and/or retrospective analyses with inherent problems. The most obvious and foremost problem with such non-randomized studies is that people, who use more sunscreen, often do so because they are, or perceive themselves to be, at increased risk of melanoma due to behavior or constitutional risk. Furthermore, most of the older studies were performed when sunscreens were neither broad spectrum, nor of high SPF value. On the other hand, one recent randomized study³⁰ of sunscreen in school children found that children using a broad spectrum SPF 30 sunscreen developed fewer nevi than did those who were not

randomized to use sunscreen (median counts, 24 vs. 28; $P=0.048$). The authors also found that sunscreen use was much more important for children with freckles than for children without and suggested that freckled children assigned to a broad-spectrum sunscreen intervention would develop 30% to 40% fewer new nevi than freckled children assigned to the control group³⁰. Since nevi are considered to be primary risk factor for melanoma, reducing the development of nevi may reduce melanoma risk. Though controversial among certain academicians, there appears to be little doubt among most clinicians and public health agencies on the value of sunscreens. Recently however, public health campaigns and physicians have advocated sunscreens as part of an overall sun avoidance program and not as a substitute for directly avoiding the sun. Indeed, it has been hypothesized that one manner by which sunscreens could increase risk of melanoma may be by reducing the sunburn associated with UVB light while allowing increased exposure time to ultraviolet light and especially harmful UVA light. UVA was not previously blocked effectively by less than broad-spectrum sunscreens and at times still may not be blocked effectively. Many current sunscreens are still not good UVA blockers. Sunscreens using physical sun-blocking products such as zinc and titanium appear at this time to provide the good broad-spectrum coverage, but may be less cosmetically appealing and therefore a combination of physical and chemical sunscreens may be best. Other research has shown that sunscreens are used incorrectly either in the amount recommended, or in the re-application rate. Thus, many believe that primary prevention campaigns should focus more on sun avoidance and protective clothing, but still recommend sunscreens as part of an overall program.

Secondary prevention programs include early detection programs. Since the outcome of melanoma is directly related to the stage at diagnosis, and since it is commonly held that melanomas take months to years to reach advanced stages, early detection has the potential to save lives. Thus, programs ranging from education of the public on self-screening and recognition of melanomas to physician screenings and screenings by other health professionals have been conducted. The effect of these programs on outcomes has not been extensively studied and there are almost no randomized trials, but there are reports of improvements in intermediate outcomes from some. Epstein et al (31) in a retrospective study of patients presenting for treatment of melanoma found that just over one half of the cancers were patient-detected (55%), but physicians were more likely to detect thinner melanomas (median thickness 0.23 mm vs. 0.9 mm; $p < 0.001$). Koh et al³² previously found that women are more likely to discover their own melanomas versus men and Epstein's study findings are in agreement with this. Studies such as these, point to the fact that often a physician or someone other than the individual with a melanoma is needed to detect it and that this may be associated with earlier-stage melanomas. The American Academy of Dermatology (AAD) has sponsored adult skin cancer screenings performed by dermatologists since 1985, resulting in more than one million screenings. Of those screened, approximately 50,000 possible non-melanoma skin cancers and 10,000 possible melanomas have been discovered. Koh et al (32) reviewed a 1986 and 1987 AAD-sponsored skin cancer-screening program in Massachusetts, which screened 2560 people³³. Of those screened, 787 (31%) were deemed to have a positive screen, which included suspected melanoma, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), dysplastic

nevus (DN), and congenital nevus (CN). They followed 22 of the 26 suspected melanomas and of these, 9 (0.35%) were actually melanomas. Of these nine melanomas, four were in situ, three were superficial spreading melanomas, one was metastatic, and the other was of unknown stage. Of note, the stage distribution of melanoma patients whose lesions were discovered by screening was improved relative to SEER records of melanomas diagnosed in the general population. Freedberg et al³⁴ using similar updated data from AAD screenings in a decision analysis found screening for melanoma to be cost-effective, in the range of \$30,000 per year of life saved. Using a decision analysis model I also recently found that melanoma screening could be cost-effective, but at a somewhat higher cost per year of life saved than found by Freedberg³⁴ (see Chapter Four). An assumption of these decision analysis studies is that the lesions detected are representative of routinely detected lesions of similar levels. If a disproportionately large percentage of the lesions detected by screening are non-aggressive and slow growing, then such decision analyses will demonstrate lower cost-effectiveness ratios than would actually occur in a true screening. There is no evidence for or against the assumption that screening may yield a higher proportion of less aggressive melanomas.

Education and self-examination are other means by which improved outcomes may be obtained. Berwick et al³⁶ in a case-control study of skin self-examination found that melanoma patients who practiced self-examination had lesions that were thinner than those who did not. In a study from Scotland, educational campaigns resulted in a reduction of tumor thickness and a trend towards improved mortality among women³⁷.

Self-examination strategies are a low-cost and seemingly viable way in which to improve outcomes among those who will do such exams. However, the proportion of individuals at risk for melanoma who can realistically be discovered and educated to do such exams prior to developing a melanoma remains unclear.

Currently only the AAD, the National Institutes of Health Consensus Conference on Early Melanoma, and the American Cancer Society recommend population-based screening. The US Preventive Services Task Force, the International Union Against Cancer, and the Australian Cancer Society do not at this time recommend routine screening for melanoma. The reason for the variability in recommendation is the lack of hard evidence from quality studies such as randomized trials. In conclusion, the facts of the melanoma epidemic are that over the last several decades there have been increases in both incidence and mortality but higher increases in incidence than mortality. Increases in incidence may be leveling off. This epidemic has arisen for a variety of reasons including: a true increase in melanomas of malignant behavior, a particularly high increase in localized and in situ lesions, and an increase in the number of biopsies performed that may have resulted in the increased detection of less aggressive lesions. The contribution of possible changes in the diagnostic criteria for melanoma to the increased incidence remains unknown. Ultraviolet light has been conclusively shown in a large number of epidemiological studies to be a factor in the increase in incidence. A variety of primary and secondary preventive strategies for controlling the problem have been attempted and may hold promise for the future. Further evaluation of these programs is warranted.

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