

D I S S E R T A T I O N

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Melanoma

*A Decision Analysis to Estimate the
Effectiveness and Cost-Effectiveness
of Screening and an Analysis of the
Relevant Epidemiology of the Disease*

Frederick Coston Beddingfield, III

RAND Graduate School

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DISSERTATION

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RGSD-167

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This document was prepared as a dissertation in September 2002 in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Policy Analysis at the RAND Graduate School. The faculty committee that supervised and approved the dissertation consisted of Emmett Keeler (Chair), Robert Brook, and Martin Shapiro.

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PREFACE

This dissertation presents a decision analysis with the aim of estimating the effectiveness and cost-effectiveness of melanoma screening by dermatologists using a visual skin exam, based on the best data available to-date. Preliminary estimates are derived and through the use of sensitive analysis, reasonable boundaries on the estimates are determined. As part of the investigation, the epidemiology of melanoma is explored, with specific emphasis on obtaining detailed estimates on the incidence and survival of melanoma, specific to age, gender, and stage at diagnosis. This investigation should be of interest to public health experts and policy makers trying to determine whether to recommend and fund melanoma screening programs, to researchers designing or deciding whether to perform a clinical trial of melanoma screening, to providers of medical care, and to the public concerned about the risk of melanoma. This dissertation is presented to the RAND Graduate School, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Policy Analysis.

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SUMMARY

Much has been written about the epidemic of melanoma in the United States and elsewhere in the world. Often debate has centered on the causes and consequences of recent epidemiological trends and even whether there truly has been an epidemic. Skin screening examinations by visual inspection are thought by many to be a reasonably simple, minimally invasive means by which melanoma morbidity and mortality could be reduced. However, some actually see increased melanoma screening as one of the causes of an apparent, though not real epidemic. Surprisingly few studies on effectiveness or cost-effectiveness of melanoma screening are available to guide policy makers on decisions regarding screening and thus there is little consensus among various groups regarding recommendations for such screening. This dissertation's main goal was to estimate the effectiveness and cost-effectiveness of melanoma screening from the best available data.

The effectiveness and cost-effectiveness of melanoma screening were estimated using a decision analysis model. The reference case model represented outpatient screening for melanoma using visual inspection of the skin by dermatologists in 1998 in a self-selected, higher-than-average-risk population by incorporating data from the American Academy of Dermatology (AAD) screenings and the National Cancer Institute's Surveillance and Epidemiology

End Results (SEER) with estimates from the literature. The AAD screening results were compared to the SEER “usual care” from the societal perspective and the results were reported as cost per year-of-life-saved (YLS). Other hypothetical cases targeting populations by age and gender were analyzed. A sensitivity analysis was performed to examine the influence of varying key estimates on the cost-effectiveness.

The results showed that one-time melanoma screening costs \$51,481 per YLS. If the additional costs of evaluating and treating non-melanoma skin cancers as part of the melanoma screening were included in the analysis, the cost increased to \$64,646 per YLS, but there would be additional non-life-saving benefits of early diagnosis and treatment of non-melanoma skin cancers. When future health costs were incorporated into the reference case analysis, the cost per YLS increased from \$51,481 to \$57,639. For a one-time screen of a self-selected population age fifty or above, the cost-effectiveness ratio was \$18,904 per YLS for men and \$30,888 per YLS for women. A one-time mass screening of the entire Caucasian population cost \$172,276 per YLS. Patients with screen-detected melanomas had an 87.8% ten-year survival versus an 83.6% ten-year survival for melanomas detected by the status quo. Screening resulted in an expected benefit of 7.76 lives not lost to melanoma over ten years and an additional eighty-seven life-years per 100,000 patients screened when compared to current care. The cost of providing the initial screen was a major determinant of the total cost of the program. The cost-effectiveness of many of these

melanoma screening scenarios fall within the range of other currently funded cancer screening programs.

As part of the goal of estimating the effectiveness and cost-effectiveness of screening, age-and gender-specific melanoma incidence and survival rates were calculated from three databases including: 1) the Surveillance Epidemiology and End Results (SEER), 2) the California Cancer Registry, and 3) the University of California at Irvine Cancer Registries for San Diego, Imperial and Orange Counties. Melanoma incidence rates are strikingly different when stratified by age and gender and these findings, which have not been reported previously, were consistent in the analyses of all three databases. The incidence of melanoma increased with age for men and women, and more specifically the following patterns were noted. Prior to the age of forty, the incidence in men and women is very similar except that women have a slightly higher rate. After age forty the incidence continues to rise at a relatively constant rate until the end of life in men, but a plateau is noted in the incidence curve in women from approximately age 45 to 60, a time that correlates roughly with menopause. During this menopausal period in women, there is little rise in incidence. After age 60 there is a slight increase in incidence with age with women, but still the rate of increase with age is not as fast as it had been prior to menopause. This distinct pattern in women was analyzed relative to melanoma histological type and the pattern is due largely to the pattern seen in superficial spreading melanomas. In addition to these findings, the results showed that not only are

men at higher risk of melanomas with age, they are also at higher risk of melanomas of advanced Breslow thickness. Women have a clearly higher rate of melanoma incidence than men only for thin lesions when under the age of forty. It is unclear whether these patterns are due to environmental, hormonal, or other possible causes. Nonetheless, the patterns are intriguing and have important implications for targeting primary and secondary melanoma prevention programs.

The results of these analyses should be seen as an attempt to use the best available data to-date in order to estimate the effectiveness and cost-effectiveness of melanoma screening and to understand factors impacting any such screening program implemented. The results described suggest that melanoma screening is likely effective and has a cost-effectiveness similar to many other cancer screening programs. Also, these findings make a strong case for a clinical trial of melanoma screening with prospective data collection given the likelihood of favorable findings. The results of these analyses could also be used to help design a study of melanoma screening, by helping to determine which groups to target in an initial study. The results suggest that using age and possibly gender would be an easy way of targeting a higher risk population with a lower study cost and a more favorable cost-effectiveness than if the general population were screened. Because the cost of the screen is a major determinant of the total costs of screening, ways in which the cost of the initial screen could be lowered should be explored as well. Ways of lowering the initial

screen costs include the use of non-dermatologists screeners such primary care physicians, specifically-trained nurses, nurse practitioners, or newer computer-assisted screening devices incorporating digital photography. A logical and consistent approach to melanoma screening will only be achieved after the necessary foundation of research has been performed. While such research is still lacking, it is hoped that this dissertation contributes substantively to the current understanding of melanoma and melanoma screening.

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INTRODUCTION

Melanoma (MM) is a serious public health problem in the U.S. and many other countries. It is the eighth most common U.S. malignancy and accounts for 1% of all cancer deaths. In addition, the incidence of melanoma has been rising rapidly, approximately 3-4% per year since the 1970s⁷. In 1935 the lifetime risk of melanoma was 1 in 1500, whereas recently it was estimated to be 1 in 75^{2,3}. This increase is due not only to earlier detection, but represents a true increase in the incidence of all stages of the disease^{2,3}. The etiology of the increase is not known with certainty but increases in ultraviolet exposure due to behavioral and ozone changes have been postulated by many⁴. The burden of disease from melanoma is high by several measures. Each year in the U.S., in addition to the approximately 40,000 incident cases, there are about 7500 deaths from melanoma. There have been increases in mortality since the 1970's, though by lesser amounts than the increases seen in incidence. More recent trends suggest the mortality rate has stabilized⁷. Each melanoma death accounts for approximately 17 years-of-life-lost on average, one of the highest rates for all adult-onset cancers¹. Not all statistics for melanoma are worsening, however. The overall survival from melanoma has increased. The 5-year survival in the 1940's was 40%, from 1980-82 it was 83%, and from 1992-98 it was 89%. This improvement in survival is thought by most researchers to be primarily due to early detection⁴. Advances in treatment have not dramatically altered the outcome for a given stage of melanoma in

recent years. Thus, primary and secondary prevention strategies have been proposed as a means to reduce the morbidity and mortality of this disease.

Primary prevention strategies aim at eliminating the causes of the disease while secondary prevention strategies aim at early detection. Both primary and secondary prevention could reduce the burden of disease from melanoma substantially. For instance, the link between sun exposure and melanoma is well-established. It has been estimated that the majority of one's lifetime sun exposure occurs by the early twenties. If so, primary prevention strategies aimed at reducing ultraviolet exposure in this young population may be successful in reducing the development of melanoma. Exactly how to go about affecting change in this population and others is an area in need of research. A recent study suggests that changing knowledge of melanoma risks such as the link between sun exposure and melanoma will be unlikely to affect behaviors dramatically without other interventions ⁶. Many researchers believe the improvements in survival of melanoma have been due to early detection and thus there is considerable interest in expanding efforts to enhance screening by self-examination and by physicians or other professionals.

Chapter Four "Estimating the effectiveness and cost-effectiveness of melanoma screening" investigates issues in secondary prevention through melanoma screening. This chapter presents a decision analysis model used to estimate the effectiveness and cost-effectiveness of melanoma screening. Because there is a significant difference in survival between early and late disease in patients with melanoma, and because some

early lesions may take months to progress to a late lesion, screening programs are thought to be a means by which melanoma outcomes may be improved. Most dermatologists assume that screening for melanoma is a useful and important service, which they provide. However, prudent health policy regarding melanoma screening is difficult to formulate at this time because of a lack of comprehensive research on the effectiveness and cost-effectiveness of such programs. Indeed, authoritative opinions vary as to the value of routine screening for melanoma. While the American Academy of Dermatology (AAD) and the American Cancer Society recommend regular skin examinations, the US Preventive Services Task Force, Australian Cancer Society, and the International Union Against Cancer do not. The Canadian Task Force on the Periodic Health Examination recommends screenings only for high-risk patients. Many important questions have not been addressed in scientific studies. These questions include: Should physician screening be performed and if so, who should be screened? Should risk factors be used to determine who gets screened and if so, which ones? Beginning at what age should people be screened? How often should people be screened? Should self-screening be promoted and if so, in what manner should it be promoted? Should non-physician health care professionals be used to screen for melanoma? The ideal study to answer these questions, a randomized, controlled clinical trial of melanoma screening, has never been performed but there are sources of data that may be helpful in answering some of these questions.

Measurements of the effectiveness and cost-effectiveness of melanoma screening programs are not available in any comprehensive manner. Given the burden of disease

from melanoma, this is surprising. Since funds spent on melanoma screening could also be spent on other cancer screening programs, it is important to determine and compare the effectiveness and cost-effectiveness of melanoma screening to screening programs for colon, breast, prostate, and other cancers. If screening programs are a cost-effective way to reduce the mortality and morbidity from this disease, they should be funded in the same manner as other funded cancer prevention and screening programs. Eventually, a large-scale, prospective, randomized screening program may be designed to estimate the cost-effectiveness of melanoma screening. However, such a costly and lengthy trial is not likely unless an estimate arrived at via other means determines it is likely to be effective and cost-effective. In addition to calculating cost-effectiveness, evaluating melanoma screening using decision analysis and modeling techniques can lead to greater insights into the design of such a trial in the future.

The characteristics of a good cancer screening program have been previously described⁵.

- 1) Screening should be highly sensitive and specific.
- 2) The prevalence of the disease should be high enough to warrant screening.
- 3) The health implications should be high enough to warrant screening.
- 4) The disease should be slowly progressing and not immediately life-threatening.
- 5) The screening procedure should be simple, inexpensive, and acceptable to the population being screened.
- 6) The disease should be one for which early diagnosis results in improved prognosis.
- 7) Screening should lead to more effective treatment at an earlier stage.

In addition to these criteria one might add that:

- 8) The population to be screened should be identifiable and reachable so as to accurately target one's screening campaign.
- 9) The campaign's cost-effectiveness should be comparable to other cancer screening campaigns.

A good case can be made that characteristics 1-3 and 5-8 are true for melanoma.

Regarding characteristic number four, the natural history of melanoma has not been clearly elucidated to-date, but melanoma likely progresses more rapidly than many other cancers and this may adversely affect number nine, the effectiveness and cost-effectiveness of screening, which is a function of the other characteristics listed. Having such an estimate is becoming more important as the cost-effectiveness is being determined for many medical interventions and is used to determine public health policy.

Cost-effectiveness calculated as YLS is one measure, perhaps the most important measure in cancer screening, but still not a complete measure of a program's worth. Further, there is often room for funding many programs geared towards different diseases, which affect health in more ways than just years-of-life saved. Nonetheless, cost-effectiveness is considered important in determining federal funding of specific health programs and when deciding where to spend the marginal dollar on health care, knowing the cost-effectiveness of potential programs can be helpful.

Some researchers have suggested the increases in melanoma incidence and improvements in survival are artifactual and due to a change in the histopathological criteria for diagnosing melanoma, such that some lesions that are biologically benign are now classified as melanoma. They suggest increased screening has led to more biopsies of these biologically benign but histologically malignant lesions thus increasing both incidence and survival⁸⁻⁹. The evidence for these hypotheses is not convincing however. Clearly, the increase in mortality is not explained by these hypotheses. These issues are analyzed in Chapters Two, "The melanoma epidemic: Res ipsa loquitur" and Chapter Three, "Gender differences in melanoma incidence". The data from these chapters were derived from analyses of the databases of the Surveillance Epidemiology and End Results (SEER) and the California Cancer Registries originally undertaken to generate parameters for modeling melanoma screening. Such necessary parameters were not available with enough specificity in the literature. An analysis of changes in incidence over time for each stage of melanoma revealed results relevant to the debate on whether there has been a "melanoma epidemic". From an analysis of incidence and life expectancy, we found important patterns of age- and gender-specific incidence not previously described for melanoma. In the final chapter, the implications of this body of research are brought into perspective. These implications are relevant to current screening policy as well as to the design of future studies. Deficiencies in our current knowledge of melanoma screening are discussed along with suggestions for future studies.

It is hoped that this dissertation will inform the debate on the effectiveness and cost-effectiveness of melanoma screening from the research currently available. Knowing that a large body of research that could guide health policy planning for melanoma screening is not currently available, it is hoped that this dissertation will also help to promote further research and guide such research appropriately.

References

1. Albert VA, Koh HK, Geller AC, et al. Years of potential life lost: another indicator of the impact of cutaneous malignant melanoma on society. *J Am Acad Dermatol* 1990;23:308-310.
2. Dennis LK. Analysis of the melanoma epidemic, both apparent and real... *Arch Derm* 1999;135:275-280.
3. Dennis LK. Increasing risk of melanoma with increasing... *JAMA* 1999;222:1037-38.
4. Langley RGB, Barnhill RL, Mihm MC, et al. Neoplasms: Cutaneous Melanoma. In Fitzpatrick's *Dermatology in General Medicine*, 5th Ed. New York: McGraw-Hill;1999.
5. McDonald CJ. Status of screening for cancer. *Cancer* 1993;72(suppl):1066- 70.
6. Santmyre BR, Feldman SR, Fleischer AB Jr. Lifestyle high-risk behaviors and demographics may predict the level of participation in sun-protection behaviors and skin cancer primary prevention in the United States: results of the 1998 National Health Interview Survey. *Cancer* 2001;92(5):1315-24.
7. Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-1999), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2001, based on the November 2000 submission.
8. Swerlick RA, Chen S. The melanoma epidemic. Is increased surveillance the solution or the problem? *Arch Dermatol* 1996 Aug;132(8):881-4.
9. Swerlick, R.A., and Chen, S. The melanoma epidemic: more apparent than real? *Mayo Clin. Proc* 1997;72:559-564.

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.

References

1. Giles G, Thursfield V. Trends in skin cancer in Australia. *Cancer Forum* 1996;20:188-91.
2. Swerlick RA, Chen S. The melanoma epidemic: more apparent than real? *Mayo Clin Proc* 1997;72(6):559-64.
3. Swerlick RA, Chen S. The melanoma epidemic. Is increased surveillance the solution or the problem? *Arch Dermatol* 1996;132(8):881-4.
4. Dennis LK. Analysis of the melanoma epidemic, both apparent and real: data from the 1973 through 1994 surveillance, epidemiology, and end results program registry. *Arch Dermatol* 1999;135(3):275-80.
5. Armstrong BK, Kricker A. Cutaneous melanoma. *Cancer Surveys* 1994;19:219-39.
6. Jemal A, Devesa S, Hartge P, Tucker M. Recent trends in cutaneous melanoma incidence among whites in the United States. *JNCI* 2001;93(9):678-83.
7. Beddingfield FC III, Cinar P, Litwack S, Ziogas A, Taylor T, Anton-Culver H. An analysis of SEER and the California Cancer Registry data on gender and melanoma incidence. Presented at the Society for Investigative Dermatology, Oral and Poster Presentation, May 2000, Washington, DC and at the Chao Family Comprehensive Cancer Center Conference on Carcinogenesis and Cancer Prevention: Non-Melanoma and Melanoma Skin Cancer. Oral presentation. Irvine, CA; June 2001. *The analyses in this reference are presented in Chapter Three.*
8. Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-1998), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2001, based on the August 2000 submission.
9. Kricker A, Armstrong BK. International trends in skin cancer. *Cancer Forum* 1996;20:192-95.
10. Holman CD, Armstrong BK, Heenan PJ, Blackwell JB, Cumming FJ, English DR, et al. The causes of malignant melanoma: Results from the West Australian Lions Melanoma Research Project. Recent Results. *Cancer Res* 1986;102:18-37.
11. Giles GG, Armstrong BK, Burton RC, Staples MP, Thirfield VJ. Has mortality from melanoma stopped rising in Australia? Analysis of trends between 1931 and 1994. *BMJ* 1996;312(7039):1121-5.
12. Lipsker DM, Hedelin G, Heid E, et al. Striking increase in thin melanomas contrasts with a stable incidence in thick melanomas. *Arch Dermatol* 1999;135(12):1451-56.
13. Burton RC, Armstrong BK. Non-metastasizing melanoma? *J Surg Oncol* 1998;67(2):73-6.
14. Burton RC, Armstrong BK. Recent incidence trends imply a nonmetastasizing form of invasive melanoma. *Melanoma Res* 1994;4(2):107-13.
15. Wingo PA, Ries LA, Rosenberg HM, et al.: Cancer incidence and mortality, 1973-1995: a report card for the U.S. *Cancer* 1998;82(6):1197-1207.
16. Hall HI, Miller DR, Rogers JD, et al.: Update on the incidence and mortality from melanoma in the United States. *J Am Acad Dermatol* 1999;40(1):35-42.
17. Lee, JAH. The relationship between malignant melanoma of skin and exposure to sunlight. *Photochem Photobiol.* 1989;50(4):493-496.
18. Wernstock M, Colditz G, Willett W, Stampfer M, Bronstien B, Mihn M & Speizer F Nonfamilial cutaneous melanoma incidence in women associated with sun exposure before 20 years of age. *Paediatrics* 1996;84:199-204.
19. Elwood JM. Melanoma and sun exposure: contrasts between intermittent and chronic exposure. *World J Surg* 1992;16:157-165.
20. Kok G & Green L. Research to support health promotion practice: A plea for increased co-operation. *Hlth Promo Int* 1990;5(4):303-8.
21. MacKie RM. The pathogenesis of cutaneous malignant melanoma. *BMJ.* 1983;287:1568-1569.
22. Green A, Williams G. UV and skin cancer: epidemiological data from Australia and New Zealand. In: Young AR, Bjorn LO, Moan J, Nultsch W, eds. *Environmental UV photobiology*. London: Plenum, 1993;233-54.
23. Mackie RM, Marks R, Green A. The melanoma epidemic. Excess exposure to ultraviolet light is established as major risk factor. *BMJ* 1996;312(7042):1362-3.

24. Tucker MA, Halpern A, Holly EA, Hartge P, Elder DE, Sagebiel RW, Guerry D 4th, Clark WH Jr. Clinically recognized dysplastic nevi. A central risk factor for cutaneous melanoma. *JAMA* 1997;277(18):1439-44.
25. Swerdlow AJ, English J, Mackie RM, et al. Benign melanocytic naevi as a risk factor for malignant melanoma. *BMJ* 1986;292:1555-1559.
26. Holly EA, Kelly JW, Shpall SN, Chiu S-H. Number of melanocytic nevi as a major risk factor for malignant melanoma. *J Am Acad Dermatol* 1987;17:459-468.
27. Garbe C, Buettner PG, Weiss J, et al. Risk factors for developing cutaneous melanoma and criteria for identifying persons at risk: multicenter case-control study of the Central Malignant Melanoma Registry of the German Dermatological Society. *J Invest Dermatol* 1994;102:695-699.
28. Slade J, Marghoob AA, Salopek TG, Rigel DS, Kopf AW, Bart RS. Atypical mole syndrome: risk factors for cutaneous malignant melanoma and implications for management. *J Am Acad Dermatol* 1995;32:479-94.
29. Greene MH, Clark WH, Tucker MA, Kraemer KH, Elder DE, Fraser MC. High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. *Ann Intern Med* 1985;102:458-65.
30. Gallagher RP, Rivers JK, Lee TK, Bajdik CD, McLean DI, Coldman AJ. Broad-spectrum sunscreen use and the development of new nevi in white children: A randomized controlled trial. *JAMA* 2000;283(22):2955-60.
31. Epstein DS, Lange JR, Gruber, SB, Mofid M, Koch SE. Is physician detection associated with thinner melanomas? *JAMA* 1999;281(7): 640-43.
32. Koh H, Miller D, Geller AC, Clapp RW, Mercer MB, Lew RA. Who discovers melanoma? *J Am Acad Dermatol* 1992;26:914-19.
33. Koh HK, Geller AC, Miller DR, Caruso A, Gage I, Lew RA. Who is being screened for melanoma/skin cancer? Characteristics of persons screened in Massachusetts. *J Am Acad Dermatol* 1991;24(2 Pt 1):271-7.
34. Freedberg KA, Geller AC, Miller DR, Lew RA, Koh HK. Screening for malignant melanoma: A cost effectiveness analysis. *J Am Acad Dermatol* 1999;41:738-45.
35. Beddingfield FC III. Is screening for melanoma cost-effective? A decision analysis. (Unpublished, in preparation).
36. Berwick M, Begg CB, Fine JA, Roush GC, Barnhill RL. Screening for cutaneous melanoma by skin self-examination. *JNCI* 1996;88(1):17-23.
37. MacKie RM, Hole D. Audit of a public education campaign to encourage early detection of malignant melanoma. *BMJ* 1992;304:1012-15.

GENDER- AND AGE-SPECIFIC DIFFERENCES IN MELANOMA INCIDENCE

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Abstract

Background and Objective Gender- and age-specific differences in melanoma incidence are poorly defined in the literature. The purpose of this study was to evaluate such gender-and age-related differences in melanoma incidence rates using large population-based U.S. datasets.

Methods Data for this study were obtained from three cancer registries: the Cancer Surveillance Program of Orange County/San Diego Imperial Organization for Cancer Control, a regional cancer registry located at the University of California, Irvine; the California Cancer Registry, comprising all regional cancer registries in the state; and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, which collects cancer data on 14% of the U.S. population. The former two

registries provided data for the years 1988-1997, while the SEER Program provided data for the years 1973-1997. Cases were stratified by age, gender, race, histologic type, location of tumor, tumor stage, and Breslow level. Age-specific incidence rates and estimated annual percentage change in incidence rates were calculated.

Results The analysis included: 6,215 melanoma and 2,195 melanoma in situ cases from the University of California, Irvine; 33,064 melanoma and 13,876 melanoma in situ cases from the California Cancer Registry; and 58,938 melanoma and 15,902 melanoma in situ cases from SEER. Incidence rates of melanoma increased with age, but more dramatic increases were seen in men relative to women after age 40. A perimenopausal plateau appeared in the melanoma incidence rate for women. Until age 40, women had a higher incidence rate of thin lesions than men; after age 40, the incidence rate of all melanomas was higher in men than in women. Melanomas in elderly men and men with thick lesions had particularly rapid rates of increase over the study period.

Conclusions Melanoma incidence rates increase with age in both genders and a perimenopausal plateau is seen in women. Men are not only at higher risk for melanoma with increasing age but are at higher risk for thick lesions.

Keywords: melanoma; melanoma incidence

Background

Melanoma is the eighth most common U.S. malignancy. It accounts for 1% of all cancer deaths and the incidence is rising. In 1935, the lifetime risk of melanoma was 1 in 1500. Americans now have a greater than 1 in 75 chance of developing a malignant melanoma. Recent results suggest significant increases in the incidence rate of melanoma and especially of early stage melanomas (1-9). Gender-specific differences in melanoma epidemiology have been studied, but few thorough analyses are available on variations in the age- and gender-specific incidence rates of this disease.

A recent analysis of data from the Surveillance, Epidemiology, and End Results (SEER) Program suggests that the incidence of melanoma increases with age with somewhat different patterns in men and women¹. Certain gender differences in melanoma epidemiology are well described, such as a predilection for limb melanomas in women and back melanomas in men, a better survival rate in women, and a greater incidence of lentigo maligna melanomas in older men. In many countries, including most European nations, the incidence of melanoma in women is higher than in men. In the United States, however, men have a higher incidence of melanoma than women. Different age- and gender-specific incidence rates may be the final product of different causal pathways and may be indicative of different potentially modifiable risk factors for malignant melanoma. Determining which subgroups of people are at particularly high risk is important for clinicians seeking to stratify their patients into different at-risk groups and educate them; to investigators trying to uncover potentially modifiable risk factors for melanoma; and to policy makers trying to decide which groups to target with public

health campaigns. One hypothesis is that these age- and gender-specific differences in melanoma epidemiology are related to changing hormonal influences, which may vary with age. Genetic or environmental interactions play a role in many cancers and may alter the age-specific incidence rates.

Objective

Our goal in this paper is to describe more clearly the age- and gender-specific incidence patterns for melanoma. This study reports on melanoma incidence rates and characterizes gender differences in melanoma in patients from three population-based cancer registries. By using population-based data, we avoided many selection biases associated with studies from referral and treatment centers. We hypothesized that there are distinct age-specific melanoma incidence patterns for men and women.

Methods

Patient Population

Patient information used in this report included melanoma cases from three sources: the Cancer Surveillance Program of Orange County / San Diego-Imperial Organization for Cancer Control (CSPOC/SANDIOCC), which is situated at the University of California, Irvine, for the years 1988-1997; the California Cancer Registry (CCR) for the years 1988-1997; and the National Cancer Institute's SEER Program, whose registries contain data from 1973-1997. The UCI data were drawn from a population of 4.76 to 5.41 million (1988 to 1997, respectively) ¹⁰; the CCR data were drawn from a population base of 28.4 to 33.0 million (1988 and 1997, respectively) ¹⁰; and the SEER

data were drawn from a population base at that time of approximately 14% of the United States population.

Study Cohort

The study cohort was composed of men and women diagnosed with melanoma of any stage or melanoma in situ as defined by the International Classification of Diseases (ICD-O) codes during the study years. Included were codes 8720-23, 8730, 8740-45, 8761, and 8770-74 with in situ lesions analyzed separately from invasive lesions.

Melanoma cases were divided into mutually exclusive age categories of <40, 40-59, and 60+ (or into other age intervals for different parts of the analysis). Race was defined by four mutually exclusive categories: non-Hispanic whites, Hispanics, blacks, and Asians. However, SEER did not begin classifying race as Hispanic and Non-Hispanic White categories until the middle of the study period. Thus, for all SEER data, "whites" included both Hispanics and Non-Hispanic whites. Stage of disease was defined as the summary stage variable in the SEER Program, which characterizes disease into three stages: localized disease, disease with regional spread, and distant/metastatic disease. Breslow thickness was analyzed as a continuous variable or separated into four categorical variables with cutoff points designated by the most recent American Joint Commission on Cancer (AJCC) guidelines. Follow-up information on all patients in the registries, including survival data, was obtained continuously regardless of whether patients were being followed for purposes of our study.

Statistical Analysis

Analyses were performed using the either SAS statistical software package or SEER*Stat (11). The estimated annual percentage change (EAPC) was calculated as described in SEER*Stat. Survival times were estimated using the Kaplan-Meier method (12). The Cox proportional hazards regression model¹³ was used to estimate the relative risk (RR) of death for each year of diagnosis and for men versus women. All statistical tests were two-tailed, with a significance level of 0.05, unless otherwise noted.

Results

General Findings and Demographics

Table 3.1 shows the characteristics of the UCI, CCR, and SEER populations. Table 3.2 summarizes gender differences noted for SEER data alone.

Age-Specific Incidence Rates

Fig. 3.1A, shows the age-specific incidence of melanoma for whites by gender using UCI data. The incidence (number of cases per 100,000 persons) of melanoma increased with increasing age during the study period for both men and women, with a more pronounced effect of age on incidence rates in men. The slopes of the age-specific incidence curves are similar for ages <40 years, but young women have a rise in incidence at an earlier age than men and maintain a higher absolute incidence of melanoma than men until approximately age 40. At approximately age 40, the age-

Table 3.1. White population characteristics of UCI, CCR and SEER databases.

Registry	UCI	CCR	SEER*
Melanoma	6215	33064	58938
Melanoma in situ	2195	13876	15902
<u>Subjects with melanoma</u>			
Male (%)	3581 (58)	19157 (58)	31180 (53)
Female (%)	2634 (42)	13907 (42)	27758 (47)
<u>Age of melanoma patients</u>			
Mean	57	56	54
Standard Deviation	36	17	18
Median	56	57	54
<u>Histology of melanomas</u>			
Malignant melanoma, NOS	2821 (45.4)	15076 (45.6)	23918 (40.6)
Superficial spreading melanoma	2145 (34.5)	11293 (34.2)	23381 (39.7)
Nodular melanoma	546 (8.8)	2922 (8.8)	5441 (9.2)
Lentigo maligna	355 (5.7)	1921 (5.8)	4100 (7.0)
Acral lentiginous melanoma	41 (0.7)	239 (0.7)	361 (0.6)
Other	307 (4.9)	1613 (4.9)	1737 (2.9)

* 1973-1997 Hispanic and Non-Hispanic whites included

specific incidence rate curves for men and women cross, and the incidence of melanoma in men diverges rapidly from women with increasing age. The maximum incidence of melanoma in white men in the UCI was 106, reached at age group 80-84 (the maximum incidence was also achieved at age 80-84 in CCR data, but at age 85+ in SEER data). The maximum incidence of melanoma was 38 for white women at age 85+ in all three databases. The incidence of melanoma in women shows a plateau in the perimenopausal period from approximately 45 to 60 years of age, during which time

Table 3.2. Summary of SEER data for Hispanic and non-Hispanic white population, 1973-1997.

	<u>Males</u>	<u>Females</u>
No. of melanomas in study (%)	31180 (53)	27758(47)
No. of melanoma in situ lesions in study (%)	8535(54)	7367(46)
Age-adjusted incidence* of melanoma	13.4	10.2
Age-specific incidence* (% All MMs)		
Age <40	4.2 (19.3)	6.0 (30.0)
Age 40-59	22.9 (36.9)	18.7 (34.7)
Age 60+	43.9 (43.8)	23.0 (35.3)
Distribution of melanoma types by histology (%)		
SSM	36.8%	42.9%
NM	10.1%	8.3%
LM	8.0%	5.8%
ALM	0.5%	0.7%
NOS	41.4%	39.6%
Other	3.2%	2.7%
Peak incidence**	58.1	29.3
Age at peak incidence**	85+	85+
Most common histology (%)		
If thin (<1 mm)	SSM (49)	SSM (51)
If thick (>4 mm)	NM (62)	NM (38)
EAPC***		
Melanoma	4.3%	3.0%
Melanoma in situ	15.8%	14.3%
* Incidence rates reported per 100,000 people ** CCR data revealed a peak incidence in non-Hispanic whites of 92 at age 80-84 in males and 33 at age 85+ for females. UCI data revealed higher peaks of 106 at age 80-84 in males and 38 at age 85+ for females. *** Estimated annual percentage change.		

the incidence remains relatively constant. To investigate this perimenopausal change in the slope of the UCI age-specific incidence curve further, we evaluated CCR and SEER data for whites (Fig. 3.1B and 3.1C, respectively). The patterns were very similar in the

three datasets, each showing a decline in the rate of increase in incidence in women after the age of approximately 45 years. The same general trends for the age-specific

Figure 3.1A. Age-specific incidence rates of melanoma in non-Hispanic whites by gender (UCI data).

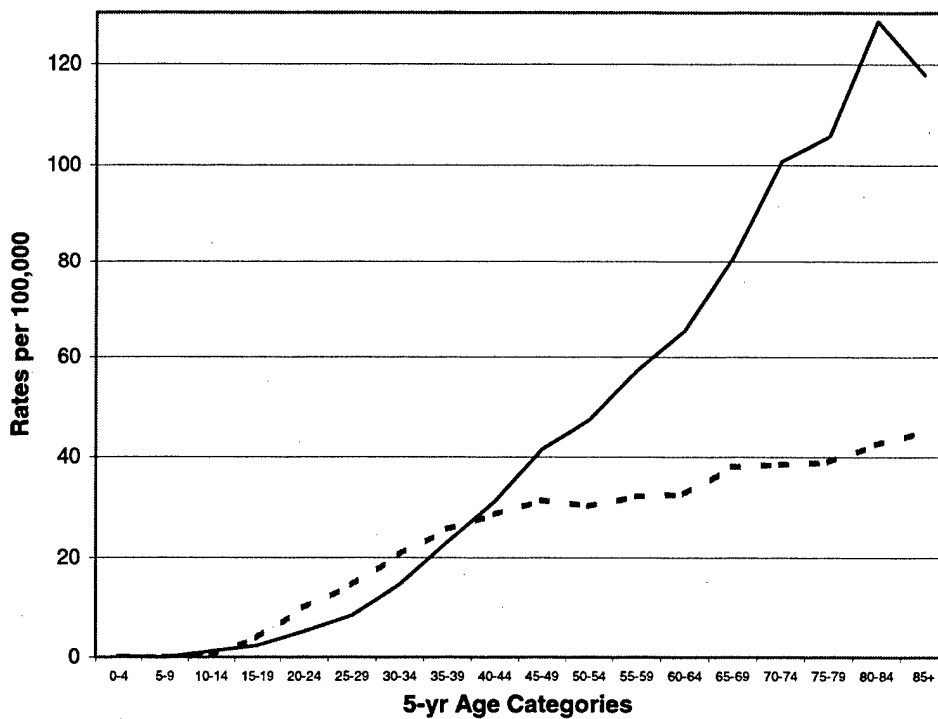


Figure 3.1B. Age-specific incidence rates of melanoma in non-Hispanic whites by gender (CCR data).

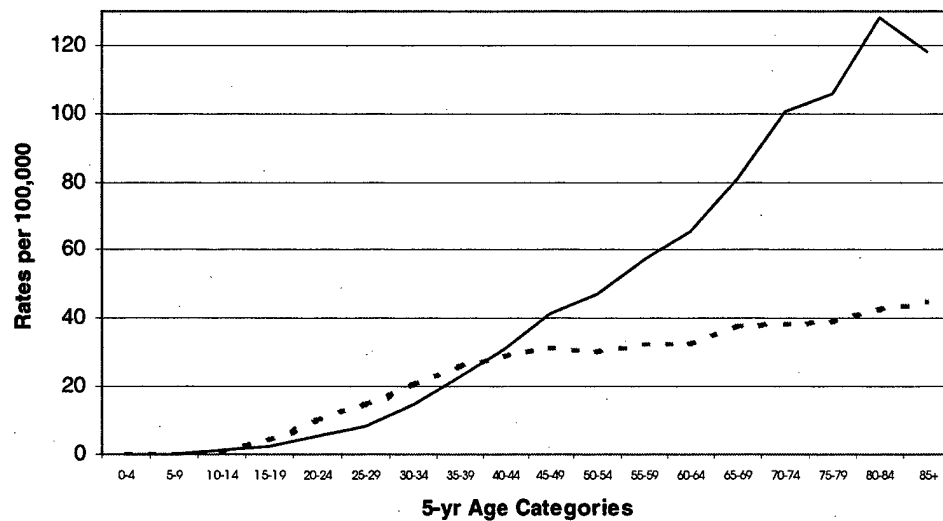
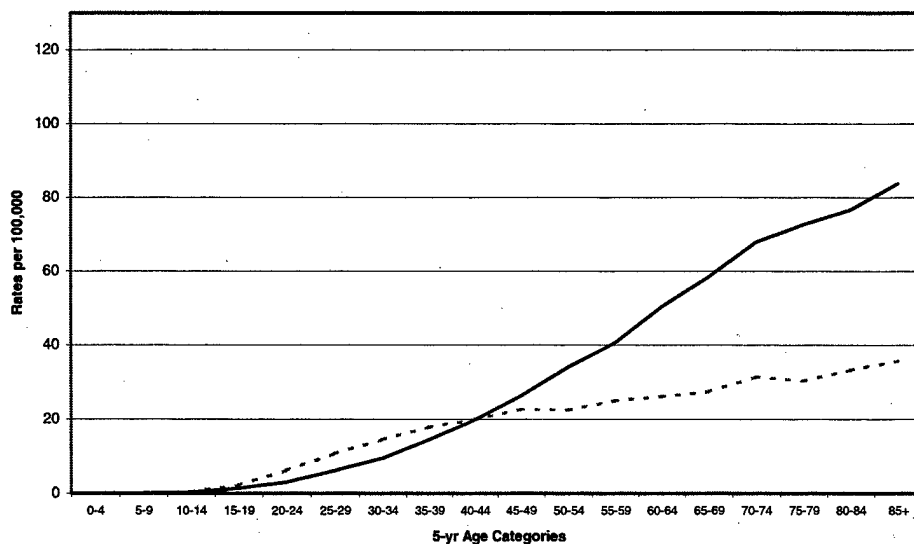


Figure 3.1C. Age-specific incidence rates of melanoma in Non-Hispanic whites by gender (SEER data).



incidence rate of melanoma were seen in the CCR and SEER datasets, though the absolute incidence was lower for any given age in SEER relative to CCR, and for any given age in CCR relative to UCI. We calculated the age-specific incidence for four-year birth cohorts in the period 1893-1957 for men and women (data not shown). The age-specific incidence was positively correlated with later birth cohort (i.e., the later one's birth in that period, the greater the incidence at any given age). The cohort effect was much stronger for groups born in the early part of the century than in the later years. In other words, the difference in age-specific incidence rates between successive four-year cohorts was greater in those born in earlier cohorts than in later cohorts.

General Findings (SEER data only)

In this study, 68% of all melanomas were thin (<1 mm), 16% were 1.0-1.99 mm in thickness, 10% were 2.0-3.99 mm, and 6% were thick (≥ 4.0 mm). Table 3.3 shows calculated incidence rates, the total number of melanomas and the number of each histologic type of melanoma, by gender and Breslow thickness. With increasing age, people had not only higher incidence rates of melanoma, but the proportion of thicker melanomas increased. The percentage of thick lesions increased with age for both men and women, but at every age men had a higher absolute incidence of thick lesions than women. For instance, when <40 years of age, women had an incidence rate of 0.12 for thick lesions, while comparably aged men had an incidence rate of 0.19. However, once age 60+, women had an incidence rate of 1.7 for lesions >4 mm (a 14-fold

Table 3.3. Age-specific incidence rates by gender, age, and Breslow levels and tumor stage (SEER 1988-1997).

	Males			Females		
Age	<40 Rate (N)	40-59 Rate (N)	60+ Rate (N)	<40 Rate (N)	40-59 Rate (N)	60+ Rate (N)
Breslow Thickness						
0-1.00	2.68 (1570)	15.1 (3442)	28.5 (3929)	4.71 (2662)	13.3 (3070)	14.2 (2655)
1.01-1.99	0.64 (375)	4.01 (915)	7.54 (1040)	0.74 (416)	2.69 (622)	3.92 (735)
2.00- 3.99	0.37 (215)	2.18 (499)	6.14 (847)	0.32 (183)	1.41 (326)	2.95 (553)
□4.00	0.19 (109)	1.08 (247)	3.94 (544)	0.12 (69)	0.63 (145)	1.72 (323)
Tumor Stage (All)						
Localized	3.60 (2112)	20.2 (4614)	35.6 (4908)	6.06 (3424)	17.3 (3999)	17.9 (3348)
Regional	0.26 (151)	1.56 (357)	4.35 (601)	0.22 (127)	0.97 (224)	2.22 (415)
Distant	0.14 (83)	1.08 (246)	2.74 (378)	0.08 (46)	0.46 (107)	1.14 (214)
SSM						
0-1.00	1.70 (997)	9.02 (2060)	13.0 (1788)	3.03 (1715)	8.55 (1976)	7.10 (1330)
1.01-1.99	0.34 (198)	1.86 (424)	2.72 (376)	0.37 (210)	1.14 (264)	1.44 (269)
2.00-3.99	0.11 (67)	0.64 (147)	1.42 (196)	0.09 (53)	0.45 (103)	0.72 (134)
□4.00	0.03 (19)	0.22 (51)	0.54 (74)	0.03 (16)	0.15 (34)	0.23 (44)
LMM						
0-1.00	0.03 (19)	0.84 (191)	5.10 (704)	0.04 (20)	0.36 (84)	2.11 (395)
1.01-1.99	0.00 (0)	0.05 (12)	0.66 (91)	0.00 (0)	0.03 (6)	0.23 (44)
2.00-3.99	0.00 (0)	0.04 (8)	0.28 (39)	0.00 (0)	0.01 (2)	0.16 (30)
□4.00	0.00 (0)	0.00 (1)	0.07 (9)	0.00 (0)	0.00 (1)	0.06 (11)
NM						
0-1.00	0.08 (45)	0.39 (90)	1.09 (151)	0.08 (48)	0.33 (77)	0.51 (96)
1.01-1.99	0.10 (56)	0.57 (131)	1.04 (143)	0.10 (54)	0.39 (89)	0.56 (105)
2.00- 3.99	0.13 (79)	0.64 (146)	2.06 (284)	0.08 (46)	0.40 (92)	0.91 (170)
□4.00	0.08 (50)	0.45 (102)	1.66 (229)	0.05 (26)	0.26 (61)	0.73 (137)

increase from age <40), and men had an incidence rate of 3.9 (a 21-fold increase from age <40 and more than double the rate in women of this age). However, women <40 had an incidence rate of thin melanomas of 4.7, almost double the rate in men (2.7). However, in people age 60+ the reverse was found, with the incidence rate of thin lesions in men exceeding that of women by a factor of two (28.5 vs. 14.2). Only for thin melanomas in people <40 years of age was the incidence rate of melanoma higher in women than men. Table 3.4A compares the ratios of incidence rates for men and women by age and Breslow thickness. Note that the male-female incidence ratios are <1 only for melanomas in people <40 with Breslow thickness <1mm. (For Breslow thickness 1.01-2.00 mm, the 95% CI includes 1.0). For all other categories the ratio is >1 and increases with increasing age or Breslow thickness. Table 3.4B compares the stage distribution of disease for men and women by age and Breslow thickness. Note that men had a higher percentage of thicker lesions and conversely a smaller percentage of thin lesions. The percent stage distributions for men and women were fairly similar in older individuals, whereas in younger individuals the distribution for men was worse than for women. Forty-two percent of all melanomas were found in people age 60+, even though this group accounts for only 16% of the relevant population. Thirty-six percent of all melanomas in women were in women 60+ and almost half (46%) of all melanomas in men were in men 60+.

Table 3.4A. Male-to-female incidence ratios by age and Breslow level (1988-1997).

	<40	40-59	60+
Breslow Level	M/F Incidence Ratio	M/F Incidence Ratio	M/F Incidence Ratio
0-1.00	0.57	1.14	2.01
1.01-1.99	0.86	1.49	1.92
2.00-3.99	1.16	1.55	2.08
≥4.00	1.58	1.71	2.29

Table 3.4B. Breslow thickness by age and gender (1988-1997).

	Males			Females		
Age	0-39	40-59	60+	0-39	40-59	60+
Breslow Level	(%)	(%)	(%)	(%)	(%)	(%)
0-1.00	69.2	67.5	61.8	79.9	73.8	62.2
1.01-1.99	16.5	17.9	16.3	12.5	14.9	17.2
2.00-3.99	9.5	9.8	13.3	5.5	7.8	13.0
≥4.00	4.8	4.8	8.6	2.1	3.5	7.6

Histology (SEER data only)

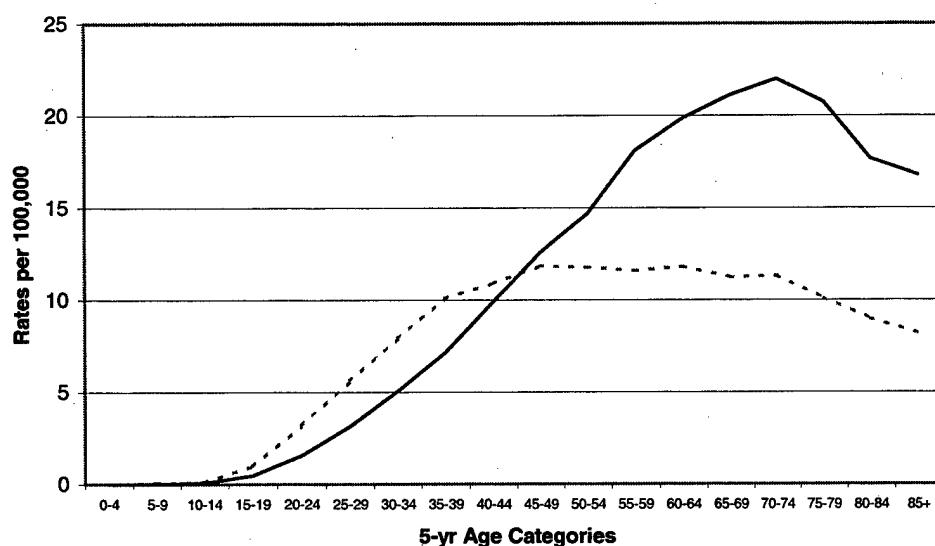
To evaluate the specific histological types of melanoma influencing the age-specific incidence curves, we evaluated such graphs for each major histological type of melanoma separately for men and women. These graphs from SEER data are seen in Fig. 3.2A through 2C, for SSM, NM, and LM. Most of the age-specific incidence graphs for each histological type of melanoma generally resemble the overall pattern seen in the age-specific incidence graphs in Fig. 3.1C. The clear exception to this is the female SSM age-specific incidence graph.

SSM accounted for 66.8% of all melanomas for which histologic type was specified², was the most common specified histologic type of melanoma in the study, and thus was an important determinant of the overall age-specific incidence graph. The overall peak incidence of melanoma of all histologic types occurred in women at the eldest age group (85+) and in men at age group 80-84. The female SSM incidence graph (Fig. 3.2A) showed a different pattern than the age-specific incidence graph for any other histologic type of melanoma including the male SSM incidence graph. The incidence of SSM increased at an earlier age than other types of melanoma, and this was especially true in women. The peak incidence of SSM reached 21 in men at age 70-74 and then declined. The peak age-specific incidence in women was 12, and was reached much earlier at age (45-49) than in men. This was followed by a plateau in the incidence of SSM in women from about age 45 to 60, and after age 60 a decline in incidence with age was noted. This pattern of SSM in women – early rise and long plateau, followed by a late-life decline – was not seen in any other histologic type of malignant melanoma. In addition, women had a significant risk of developing an SSM at an early age. By age 20-24, the incidence rate of SSM in women was 3, whereas in the female age-specific incidence graph for NM, such a rate was not reached until age 75-79, at which point the female SSM graph was reaching the end of the plateau. The incidence rates of both

² Note that this percentage is *only for melanomas in which histology was specified* and this differs from the percentages listed in Table 2. In Table 2, “melanomas, not otherwise specified” are included in the calculation of the percentages. This same is true for the subsequent paragraphs describing nodular melanoma and lentigo maligna melanoma percentages.

NM and lentigo maligna melanoma rose with age, but the rise in incidence rate began at a much later age (by 20-30 years) compared to SSM. Furthermore, no plateau was seen with the age-specific incidence for NM or lentigo maligna melanoma.

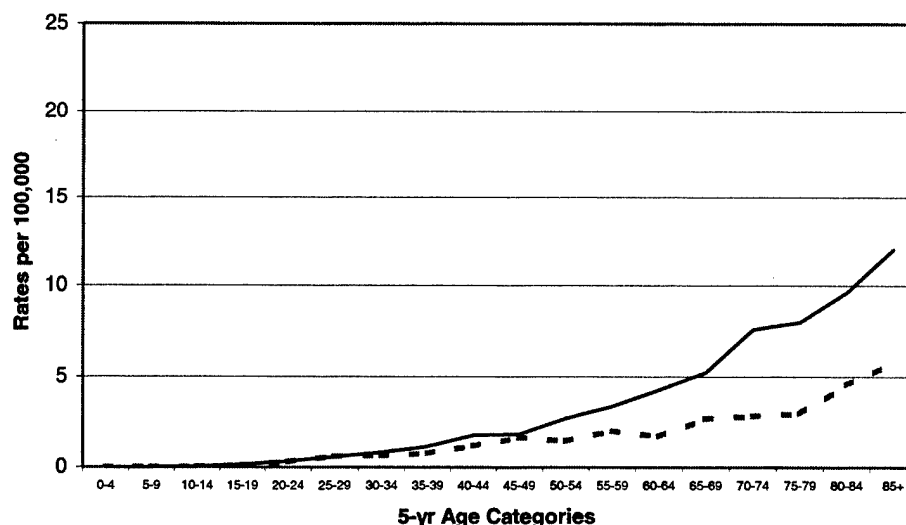
Figure 3.2A. Age-specific incidence rates for superficial spreading melanoma in Hispanic and Non-Hispanic whites by gender (SEER data).



NM accounted for 15.5% of all melanomas for which histologic type was specified. In Fig. 3.2B, note that the incidence of NM in both men and women increased continually with age, and thus the peak for both genders was reached in the final age group (85+). Unlike SSM, the NM age-specific incidence graph for women showed a long initial period of almost no change in incidence rate with age, which was followed by a relatively late increase in the slope of the age-specific incidence curve, at approximately

age 60. Before age 60 the incidence increased from 0 to 2. From ages 60 to 85+, the incidence in women increased from 2 to approximately 6 per 100,000. In men the incidence of NM began to rise at about age 45. From ages 45 to 85+, the age-specific incidence of NM in men increased almost six-fold, from approximately 2 to 12.

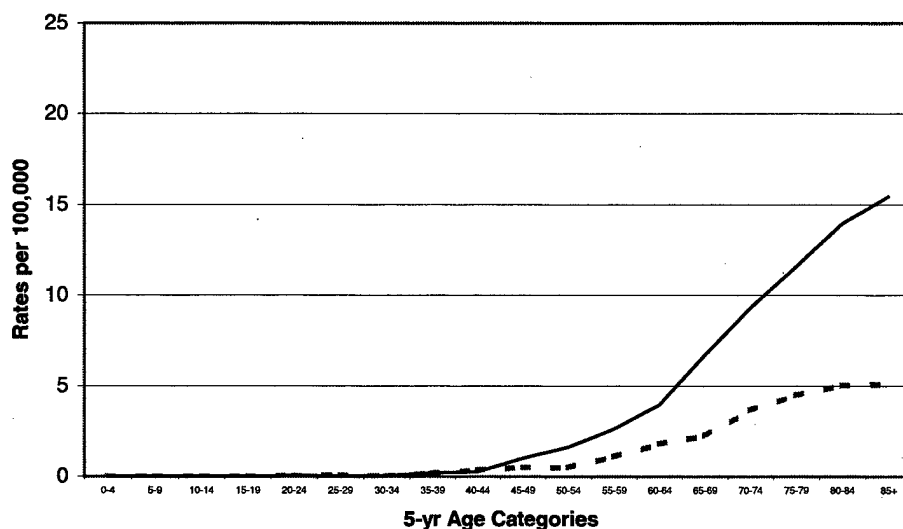
Figure 3.2B. Age-specific incidence rates for nodular melanoma in Hispanic and Non-Hispanic whites by gender (SEER data).



Lentigo maligna melanoma accounted for 11.7% of all melanomas for which histologic type was specified. The incidence rate of lentigo maligna melanoma (see Fig. 3.2C) was almost negligible in men before age 40 and in women before age 55. From age 40 to age 85+ the age-specific incidence in men increased more than 40-fold, from 0.35 to 15. The disparity in the incidence in men relative to women was also notable in lentigo

maligna melanoma, where men by age 85 had an incidence three times as high as that in women (5 vs.15).

Figure 3.2C. Age-specific incidence rates for lentigo maligna melanoma in Hispanic and Non-Hispanic whites by gender (SEER data).



We examined histological-type relative to gender, age, and Breslow thickness in whites using SEER data. Men accounted for 53% and women for 47% of all melanomas. Thin melanomas were more likely to be SSM (56%) and thin melanomas were slightly more common in women than in men (51% versus 49%). Thick melanomas were more likely to be NM (NM accounted for 9.2% of all melanomas, but 42% of thick melanomas). Men accounted for 62.6% of all thick melanomas. Fifty-seven percent of thin melanomas were SSM, but only 2.9% were NMs. In contrast, only 17% of thick melanomas were SSM, but 42% were NM. Lentigo maligna melanomas showed a

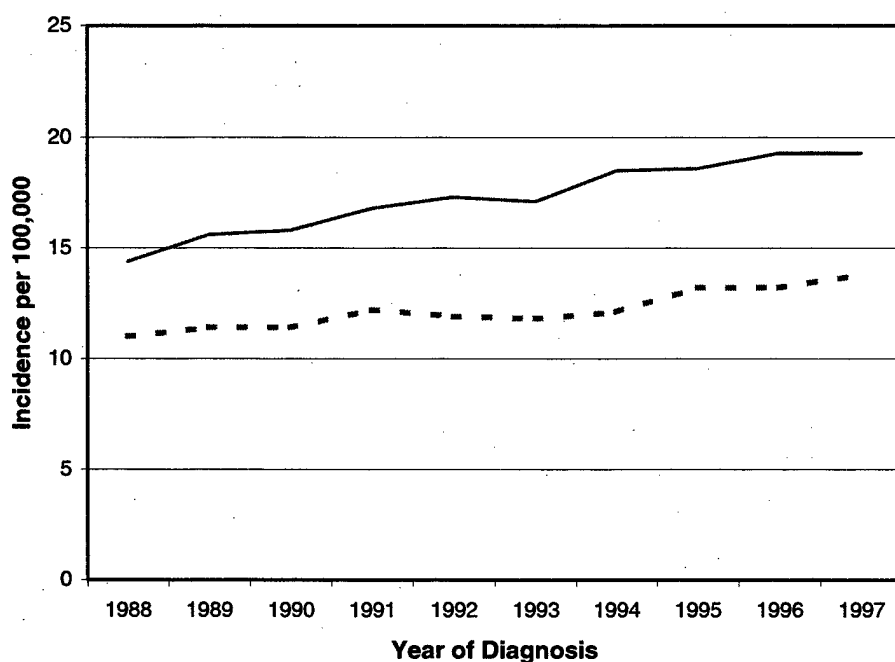
clear male predominance, with 64% of all lentigo maligna melanomas being diagnosed in men.

Estimated Annual Percentage Increase (SEER data only)

Fig. 3.3 shows the age-adjusted incidence rates of melanoma by year of diagnosis from SEER data. Incidence rates increased at a fairly constant rate for most of the study but the rate of increase appeared to slow slightly in the last two years (1996-1997). The percent change in incidence of melanoma also varied by gender. Incidence rates for all subjects showed an EAPC of 3.2 from 1988 to 1997 (UCI data) and an EAPC of 3.7 (SEER data) from 1973-1997. From 1973-1997 melanomas in men increased at a rate of 4.3% per year, while the rate in women increased at a lower rate of 3.0% (SEER data). Melanomas in situ increased at a rate much greater than melanomas (EAPC 15.1 vs. 3.7 per year). A similar pattern was seen in CCR data for non-Hispanic whites (EAPC 9.6 for melanomas in situ vs. 2.1 for melanomas) from 1988-1997. The EAPC in melanoma and melanoma in situ for both men and women increased with age, but young women had higher rates of increase than young men, while older men had higher rates of increase than older females. Perhaps most notable is that the rate of increase of thick lesions in men was remarkably high (EAPC 6.8), while the incidence of thick lesions did not increase in women (EAPC 1). In men, lentigo maligna melanomas increased at the highest rate (EAPC 10.0) followed closely by SSM (EAPC 9.8), whereas in women the increase was greatest for SSM (EAPC 9.0), with a somewhat lower but notable increase in lentigo maligna melanomas (EAPC 5.6).

The incidence rates of melanoma differed in men and women by location on the body. Men developed slightly more malignant melanomas on their torso than any other location. On the other hand, women developed substantially more (almost twice as many) melanomas on their limbs than elsewhere (UCI data, not shown).

Figure 3.3. Age-adjusted incidence rates of melanoma by year of diagnosis, 1988-1997 (SEER data).



Conclusions

In this population-based study using the UCI, CCR, and SEER databases with data for more than 100,000 separate melanoma and melanoma in situ cases, we have noted several important gender differences in the incidence rates. Both men and women have increases in the incidence of melanoma with age, but the patterns are quite different. In

men, the incidence of melanoma dramatically increases with age and continues until virtually the end of life. In women there is a plateau or leveling off of the rate of increase in incidence with at approximately age 45. This plateau and many of the differences in the incidence of melanoma between men and women are predominantly explained by the very different age-specific incidence pattern of SSM in women. In addition to the having higher incidence of melanoma with age, men are particularly at risk for tumors of increased thickness. The only subgroup in which women have a clearly higher incidence of melanoma than men is in the group <40 years of age with thin lesions, where the incidence in women is twice that of men. The vast majority of melanomas in young women are thin. However, even among the < 40 year old group, men have higher rates of thick lesions and metastatic lesions than women. Both melanoma and melanoma in situ incidence increased over time during the study period, but melanoma in situ increased at an annual rate dramatically higher than that of melanoma.

This study of three population-based datasets with large sample sizes confirms that there are clear gender differences in the age-specific incidence rates of melanoma. The use of large population-based data and the finding of similarities between the nationally representative SEER database and the CCR dataset suggest that our results are fairly generalizable within the United States. The age-specific incidence was less for whites in SEER relative to CCR, relative to UCI, and this may relate to environmental differences related to latitude, lifestyle differences, and the inclusion of Hispanic whites from the whites category in SEER. Previously, it had been thought that the age-specific incidence rate of melanoma increased until middle age and then leveled off. In fact,

while both men and women have increases in the incidence rate of melanoma with age, the incidence rate in men continues to increase after age 40, while the incidence rate in women begins to plateau by age 45 correlating with the perimenopausal period.

Clearly, no such plateau is seen in men. In men from age group 40-45 to age group 85+, the incidence rises dramatically, more than four-fold on average while in women the change in incidence over the same ages is approximately 50%. In all three datasets, the rate of increase in incidence with age (i.e., the slope of the age-specific incidence curve) in the postmenopausal period in women never returns to the premenopausal rate of increase. Rather, a more gradual increase with age is seen postmenopausally.

Though the cause of this female perimenopausal plateau in the age-specific incidence of melanoma is unknown, some potential causes may include a transient hormonal or other menopausal influence on the development of melanoma, the waning of a melanoma-promoting premenopausal hormone, a population-specific finding such as a birth cohort effect, or environmental factors such as differing exposure patterns to ultraviolet light. Given the known changes in hormone levels during menopause, it is plausible that a hormonal influence may be involved, but there are somewhat contradictory findings. One hypothesis is that the plateau could result from the waning of a melanoma-promoting premenopausal hormone. For instance, if estrogen or another hormone were promoting the occurrence of melanoma in premenopausal women, a diminishing amount of this hormone in perimenopausal women could account for such a diminishing rate of increase in incidence rate. It is known that estrogen and

progesterone levels decline during menopause. However, this hypothesis is confounded by the fact that these hormones decrease even further in the postmenopausal period. Thus, if declining levels of some hormone were solely responsible for this plateau, we might logically expect an even further decline in the incidence rate of female melanoma postmenopausally, with ages 45-60 representing an intermediate phase. But this is not seen. Rather, the incidence of melanoma increases, albeit gradually, after menopause. On the other hand, if a large fraction of women are placed on hormone replacement therapy postmenopausally, one could account for the postmenopausal rise in incidence, though at a lesser rate of increase than premenopausally. This hypothesis could be tested in a database in which the hormone replacement therapy status of a population and melanoma patients was known. It is also possible that an age-related increase in incidence occurs despite what would otherwise be a hormone-related decline in incidence postmenopause.

Perhaps even more important, if estrogen and progesterone were the predisposing hormones, rising levels of these hormones in pregnancy or in patients receiving exogenous hormones might be expected to raise the incidence of melanoma in these subgroups. However, to date, evidence on the role of gender and endogenous and exogenous hormones on the development of melanoma has been contradictory¹⁴⁻²⁴, with the majority of studies finding no increased risk of occurrence in pregnancy or in women taking exogenous hormones. Initial studies suggested a role of oral contraceptives in the development of melanoma; however, later systematic reviews of melanoma studies were unable to confirm such an association. There are pigmentary

changes associated with some women during pregnancy that may suggest a hormonal effect on melanocytes, but the exact role of hormones on nevi and melanoma is not certain¹⁴⁻²⁴. The median thickness of melanomas diagnosed during pregnancy is greater than site-matched melanomas in non-pregnant women²³. However, survival for a melanoma of a given thickness compared to site- and age-matched controls is the same regardless of pregnancy²³. It is known that a proportion of melanoma cells carry estrogen type II receptors, but their function is uncertain²⁴. There are no reports to date of an independent influence of menopause on melanoma incidence rate, though one report noted a significant interactive effect of menopausal status with body mass index on melanoma incidence rate¹⁴. In that study, melanoma cases were three times more likely than controls to be obese and to have already passed through natural menopause, but the significance of this finding is unclear. In summary, though it is possible, it is not at all clear that hormones play a role in the development or behavior of melanomas, nor do they readily account for the perimenopausal plateau in the incidence rate of melanoma in women. To examine these findings further, studies would need to correlate actual endogenous and exogenous hormone levels with melanoma incidence and further separate age-effects from hormone-effects.

An age-effect could explain the fact that the age-specific incidence rate continues to rise, albeit at a slower rate after this perimenopausal reduction. In fact, most cancers rise with age for a variety of reasons such as a decline in the immune tumor surveillance, a reduction in DNA repair, latency periods between inciting environmental injuries and tumor occurrence, and multiple other factors. But why do men have such a

dramatically higher incidence rate of melanoma than women after age 40? There appears to be a dramatically differential effect of age on incidence rate of melanoma by gender and the reason for this is not clear.

A birth cohort effect seems unlikely to account for much of the gender differences seen. In a letter to editors of the Journal of the American Medical Association²⁵, Dennis depicted a graph of melanoma incidence rates by age using SEER data. In this study, the incidence rate of melanomas in women at first appears to increase steadily and minimally until midlife and then levels off. However, when birth cohort is controlled for, the incidence rate appears to increase slowly until age 60-65 in women, after which time it appears to rise much faster. Thus, the author found that controlling for birth cohort revealed a more dramatic increase of melanoma incidence rate with age in both men and women, but certainly no plateau. In our evaluation of birth cohort, we found no evidence for a birth cohort effect accounting for the plateau in the age-specific incidence rate of melanoma in women after age 40. No plateau was seen in men in our analysis and thus any birth cohort effect accounting for the female plateau would have to be specific to the female birth cohort. Furthermore, given Dennis' findings, controlling for birth cohort could potentially make the plateau and the subsequent age-specific increase in melanoma even more pronounced. Thus, it seems unlikely that a birth cohort effect accounts for the plateau in the incidence rate of melanoma in women.

Consistently studies point to a major role of ultraviolet light exposure as the most important risk factor for melanoma in those with phenotypic susceptibility²⁶⁻³². One very

plausible explanation for part of the gender differences seen is that men and women have different environmental exposure patterns, namely ultraviolet light exposure. This could happen if men continue sun exposure later in life, but women have high sun exposure early in life yet reduce sun exposure after early adulthood. This hypothesis suggests total lifetime sun exposure is very important in determining the development of melanoma as opposed to the commonly held belief that early adulthood is the more important period for ultraviolet damage resulting in melanoma²⁵. Certainly it is clear from our data that men get more lentigo maligna melanoma in later age than women, and lentigo maligna melanoma is the melanoma type with the most direct relationship to continuous sun exposure. However, in this study we have shown that the gender differences in incidence of melanoma in later age are due predominantly to the different age-specific incidence pattern of SSM in women. SSM make up approximately 63% of all specified melanomas in our data and thus are a primary determinant of the overall shape of the age-incidence curve. The development of SSM appears most related to intermittent sun exposure³³. Given the unique shape of the SSM age-specific incidence curve in women, this is probably largely responsible for the plateau in the rate of increase in incidence in women after age 40. SSM is by far the most common type of melanoma, for men and women, even in later age. In this study one of the interesting findings, which goes against conventional wisdom, is that SSM is quite common in men even in later age, and the peak incidence occurs at age 70-74. A current edition of a leading dermatology textbook states that the average age at diagnosis of SSM is in the fourth to fifth decades³³. Though this may be true, it does not adequately convey the age-related risk of SSM for men, since the incidence in the mid 70s is almost twice that

in the mid 40s. If increased sun exposure in men relative to women in midlife is responsible for the differences in the incidence of melanoma after age 40, this could imply that sun exposure after childhood and early adulthood is more important than previously recognized. Such a finding would rightly give even more credence to public health messages advising sun protection and sun avoidance at all ages.

One implication of the finding that men older than age 60 have such a remarkably high incidence of melanoma, particularly thick melanomas, is that this may be one group who could benefit from interventions such as educational campaigns or screenings. In Table 3.4 it is remarkable how the ratio of male-to-female incidence rates increases in an incremental fashion from about 0.6 in thin lesions in people <40 to greater than 2 as one moves toward older patients or toward thicker lesions. Thus, older males are a distinctly high-risk group and may be particularly suitable to screening or other early detection interventions. Research into why this group is at such high risk and how best to intervene is warranted.

What has caused the increase in the incidence of melanomas? Perhaps the most likely answer, though not directly a part of this research, is increased exposure to ultraviolet light correlating with lifestyle changes. Numerous studies from many countries have linked melanoma to ultraviolet exposure in a variety of ways²⁷⁻³⁶. 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 depletion³⁴⁻³⁶. The exposure to ultraviolet light may well have occurred years or decades prior to the

detection of disease, though more research in this area is needed. Interventions aimed at reducing the mortality and morbidity of melanoma will inevitably be multifaceted and may include educational campaigns aimed at changing behaviors (sun avoidance for example) and early detection, either by oneself or health practitioners.

In this study we confirm recent data suggesting that the incidence rate of melanoma increases with increasing age, and we have found in women a perimenopausal plateau after which the incidence of melanoma increases less rapidly with age. This is in distinct contrast to men, where the incidence of melanoma continues to increase rapidly after age 40. We also note that men are not only at increased risk of melanoma with increasing age, but are also at risk for thicker melanomas with greater age. This finding has significant implications for targeting elderly men in public health interventions such as educational or screening campaigns. Our findings of age- and gender-specific incidence patterns and a perimenopausal plateau in women raise further questions about the possible different gender-specific environmental and hormonal influences on melanoma development and warrant further investigation.

References

1. Dennis, L.K. Analysis of the melanoma epidemic, both apparent and real: Data from the 1973 through 1994 surveillance, epidemiology, and end results program registry. *Arch Dermatol* 1999; 135: 275-280.
2. Lipsker, D.M., Hedelin, G., Heid, E., Grosshans, E.M., and Cribier, B.J. Striking increase of thin melanomas contrasts with a stable incidence of thick melanomas. *Arch Dermatol* 1999;135:1451-1456.
3. Swerlick, R.A., and Chen, S. The melanoma epidemic: is increased surveillance the solution or the problem? *Arch Dermatol* 1996;132:881-884.
4. Swerlick, R.A., and Chen, S. The melanoma epidemic: more apparent than real? *Mayo Clin. Proc* 1997;72:559-564.
5. Lamberg L. "Epidemic" of malignant melanoma: true increase or better detection. *JAMA* 2002; 287(17):2201.
6. Beddingfield FC, III. The melanoma epidemic: Res ipsa loquitur. *Onc Spectr* 2002;3(4):249-254.
7. MacKie, R.M., Hole, D., Hunter, J.A., Rankin, R., Evans, A., McLaren, K., Fallowfield, M., Hutcheon, A., Morris, A. Cutaneous malignant melanoma in Scotland: incidence, survival, and mortality, 1979-94. *BMJ* 1997;315:1106-1107.
8. MacLennan, R., Green, A.C., McLeod, G.R., Martin, N.G. Increasing incidence of cutaneous melanoma in Queensland, Australia. *JNCI* 1992;84:1427-1432.
9. Hiatt, R.A., Fireman, B. The possible effect of increased surveillance on the incidence of malignant melanoma. *Prev Med* 1986;15:652-60.
10. State of CA, Department of Finance, Race/Ethnic Population and Sex Detail, 1970-2040. Sacramento, CA, 1998.
11. SEER*Stat 4.0.9, Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-1998), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2001, based on the August 2000 submission.
12. Kaplan, E.L., and Meier, P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-481.
13. Cox, D.R. Regression models and life tables. *JR Stat Soc* 1972;34:187-220.
14. Smith, M.A., Fine, J.A., Barnhill, R.L., and Berwick, M. Hormonal and reproductive influences and risk of melanoma in women. *Int. J Epidemiol* 1998;27:751-757.
15. Holman, C.D., Armstrong, B.K., and Heenan, P.J. Cutaneous malignant melanoma in women: Exogenous sex hormones and reproductive factors. *Br J Cancer* 1984;50:673-680.
16. Gallagher, R.P., Elwood, J.M., Hill, G.B., Coldman, A., Threlfall, W., and Spinelli, J. Reproductive factors, oral contraceptives and risk of malignant melanoma: Western Canada Melanoma Study. *Br J Cancer* 1985;52:901-907.
17. Green, A., and Bain, C. Hormonal factors and melanoma in women. *Med J Aust* 1985;142: 446-448.
18. Osterlind, A., Tucker, M.A., Stone, B.J., and Jensen, O.M. The Danish case-control study of cutaneous malignant melanoma. III. Hormonal and reproductive factors in women. *Int J Cancer* 1988;42:821-824.
19. Zanetti, R., Frahceschi, S., Rosso, S., Bidoli, E., Colonna, S. Cutaneous malignant melanoma in females: the role of hormonal and reproductive factors. *Int J Epidemiol* 1990;19:522-526.
20. Holly, E.A., Cress, R.D., and Ahn, D.K. Cutaneous malignant melanoma in women. III. Reproductive factors and oral contraceptive use. *Am J Epidemiol* 1995;141:943-950.
21. Gefeller, O., Hassan, K., and Wille, L. Cutaneous malignant melanoma in women and the role of oral contraceptives. *Br J Dermatol* 1998;138:122-124.
22. Pfahlerberg, A., Hassan, K., Wille, L., Lausen, B., and Gefeller, O. Systematic review of case control studies: oral contraceptives show no effect on melanoma risk. *Public Health Rev* 1997; 25: 309-31
23. Mackie RM. Pregnancy and exogenous hormones in patients with malignant melanoma. *Curr Opin Onc* 1999;11:129-131.5.
24. Neifeld JP, Lippman ME. Steroid hormone receptors and melanoma. *J Invest Dermatol* 1980;74: 379-81.

25. Dennis, L.K. Increasing risk of melanoma with increasing age. *JAMA* 1999;282:1037-1038.
26. Kricker, A., Armstrong, B.K., Jones, M.E., Burton, R.C. Health, solar UV radiation, and environmental change. Lyon, France: International Agency for Research on Cancer; 1993.
27. Wernstock M, Colditz G, Willett W, Stampfer M, Bronstien B, Mihm M, & Speizer F. Nonfamilial cutaneous melanoma incidence in women associated with sun exposure before 20 years of age. *Paediatrics* 1996;84:199-204.
28. Elwood JM. Melanoma and sun exposure: contrasts between intermittent and chronic exposure. *World J Surg* 1992;16:157-165.
29. Kok G & Green L. Research to support health promotion practice: A plea for increased co-operation. *Hlth Promo Int* 1990;5(4):303-8.
30. MacKie RM. The pathogenesis of cutaneous malignant melanoma. *BMJ* 1983;287:1568-1569.
31. Green A, Williams G. UV and skin cancer: epidemiological data from Australia and New Zealand. In: Young AR, Bjorn LO, Moan J, Nultsch W, eds. Environmental UV photobiology. London: Plenum, 1993;233-54.
32. Mackie RM, Marks R, Green A. The melanoma epidemic. Excess exposure to ultraviolet light is established as major risk factor. *BMJ* 1996; May 25;312(7042):1362-3.
33. Langley RGB, Barnhill RL, Mihm MC, et al. Neoplasms: Cutaneous Melanoma. In Fitzpatrick's Dermatology in General Medicine, 5th ed. New York: McGraw-Hill; 1999.
34. Wingo PA, Ries LA, Rosenberg HM, et al.: Cancer incidence and mortality, 1973-1995: a report card for the U.S. *Cancer* 1998;82(6):1197-1207.
35. Hall HI, Miller DR, Rogers JD, et al.: Update on the incidence and mortality from melanoma in the United States. *J Am Acad Derm* 1999;40(1):35-42.
36. Lee, JAH. The relationship between malignant melanoma of skin and exposure to sunlight. *Photochem Photobiol* 1989;50(4):493-496.

**ESTIMATING THE EFFECTIVENESS AND
COST-EFFECTIVENESS OF MELANOMA SCREENING**

Abstract

The purpose of this study was to estimate the cost-effectiveness of melanoma screening programs. A decision analysis model was used to estimate the cost-effectiveness of a hypothetical melanoma screening program by dermatologists in 1998 in a self-selected (higher-than-average-risk) population by comparing data on melanomas diagnosed in screenings by the American Academy of Dermatology (AAD) screenings with data on melanomas diagnosed by current care (largely without special screenings) as reported to the Surveillance, Epidemiology, and End Results (SEER)⁸² program. The analysis was performed from a societal perspective and the results were reported as cost per year-of-life-saved (YLS). Further analyses evaluated screens in specific sub-groups at varying risk for melanoma and another analysis modeled mass screening of the entire Caucasian population. A sensitivity analysis was performed to determine the influence of varying key estimates on the cost per YLS. The results showed that a one-time melanoma screening costs \$51,481 per YLS. If the additional costs of evaluating and treating non-melanoma skin cancers as part of the melanoma screening were included in the analysis, the cost increased to \$64,646 per YLS, but there would be additional non-life-saving benefits of early diagnosis and treatment of non-melanoma skin cancers. For a one-time screen of a self-selected population age

fifty or above the cost-effectiveness ratio was \$18,904 per YLS for men and \$30,888 per YLS for women. A one-time mass screening of the entire Caucasian population cost \$172,276 per YLS. Patients with screen-detected melanomas had an 87.8% ten-year survival versus an 83.6% ten-year survival for melanomas detected by the status quo and an expected benefit of 7.76 lives not lost to melanoma per 100,000 patients over ten years when compared to current care. The cost of providing the initial screen was a major determinant of the cost of the program. The cost-effectiveness of many of these melanoma screening scenarios fall within the range of other currently funded cancer screening programs. A trial of melanoma screening with prospective data collection on cost effectiveness should be performed.

Introduction

Melanoma (MM) is the eighth most common US malignancy and accounts for 1% of all cancer deaths. In addition, the incidence of melanoma has been rising⁸³. In recent years over 7,000 deaths per year have been reported due to melanoma⁸³. In 1935 the lifetime risk of melanoma was 1 in 1500, whereas now it is 1 in 75¹⁵, an approximate 5% increase per year. The increase is due not only to earlier detection, but represents a true increase in the incidence of the disease. Each melanoma death has been reported to result in an average of 17.1 years of potential life lost, which is one of the highest rates for adult-onset cancers². Because survival differences between early disease and late disease in patients with melanoma correlate very well with stage at diagnosis, it is believed that earlier diagnosis and treatment interventions should yield improved survival. Early lesions may take months or even years to progress to a late lesion, and

thus screening programs which may detect lesions at an earlier stage are often touted as a means by which melanoma outcomes may be improved. In fact, melanoma has many traits that might make it suitable to screening. The disease burden is high. The screening exam is non-invasive, easy to perform, and inexpensive. The sensitivity of the exam is good when performed by dermatologists^{31,40, 54-55, 57, 80}. Detected early, the disease has an excellent prognosis, while detected late the prognosis is dismal. Other aspects of the disease such as the natural history are not known with certainty.

However, prudent health policy regarding melanoma screening is difficult to formulate at this time because of a lack of comprehensive research on the effectiveness and cost-effectiveness (CE) of such programs. Indeed, authoritative opinions vary as to the value of routine screening for melanoma. While the American Academy of Dermatology (AAD) and the American Cancer Society recommend regular skin examinations, the US Preventive Services Task Force, Australian Cancer Society, and the International Union Against Cancer do not recommend routine screening for melanoma. The Canadian Task Force on the Periodic Health Examination recommends skin examinations only for high-risk patients.

Measurements of the cost-effectiveness of melanoma screening programs, such as cost per year-of-life-saved (YLS), are not available in any comprehensive manner and no randomized controlled trials of melanoma screening programs exist. Since funds spent on melanoma screening could also be spent on various interventions including other cancer screening programs, it is important to determine and compare the cost-effectiveness of melanoma screening to the cost-effectiveness of other screening

programs and perhaps the best comparisons are with screening programs for colon, breast, cervical, and prostate cancers. While recommendations regarding screening remain controversial at this time, screening programs may be a cost-effective way to reduce the mortality and morbidity from this disease. If so, one can argue they be funded in much the same manner as other currently funded cancer screening programs. Eventually, a large-scale, prospective, randomized screening trial may be conducted to estimate the cost-effectiveness of melanoma screening. Such a trial should be considered ethical given that the current default standard is not to screen for melanoma. However, such a costly and lengthy trial could be better planned and a better case made for such a trial if a decision analysis model determines screening is likely to be effective and cost-effective.

Previous Studies

There have been no randomized controlled trials, relatively few reports of the results of melanoma screening programs in general, and no studies on the cost-effectiveness of melanoma screening programs aside from a recent study by Freedberg et al³¹ and another in Australia by Grigis et al³⁷.

Freedberg et al³¹, in an interesting study calculated a cost-effectiveness ratio of \$29,170 per YLS for a one-time screening program of self-selected, high-risk patients with a mean age of 48 years. This estimate included the induced costs of the detection and treatment of non-melanoma skin cancer (NMSCA) during the melanoma screening. Cost estimates came from 1993 HCFA reimbursements and parameters for the

effectiveness of screening came from an analysis of AAD screening programs for the screened branch and 1990 SEER data for the non-screened branch. The screened group was self-selected and at higher-than-average risk^{31,36,56}. Because the population who received AAD screenings were self-selected, it is possible that differences seen in the stage of distribution of melanomas between the screened AAD group and “unscreened” SEER group were due in part to differences in the groups besides the screening itself. Screening remained below \$50,000/YLS if the prevalence of melanoma in the screened population remained at least 90 per 100,000, 98.4% of detected melanomas were localized, and the cost of the initial screen was below \$57. In this model, screening made a difference for those 5 percent of patients (by the authors’ assumptions and calculations) who if screened, would have been detected with localized disease, but if not screened would have developed metastatic disease. The authors did not examine the results in a model that evaluated a step-wise progression through the Breslow stages of localized disease into regional and metastatic disease and the authors only evaluated a one-time screen. From the methods section, it is not clear if their model directly accounts for potential age-and gender-related differences in melanoma incidence and survival and benefits from screening across a spectrum of ages. The authors did not calculate age-or gender-specific cost-effectiveness estimates for melanoma screening in their study. Such estimates would be useful in determining a coherent screening strategy, which may use age or gender as or factor when deciding who should be screened. Regarding costs, the authors appear to have considered direct medical costs of evaluation and treatment but not costs for terminal care or increased future care because of lives saved. The cost estimates the authors used for

melanoma patients are low compared with a recently published article estimating the costs of melanoma evaluation and treatment⁸⁸. Despite some drawbacks however, this paper appears to provide the best estimate of the cost-effectiveness of melanoma screening available to-date.

Girgis et al³⁷ in 1996 published a cost-effectiveness study of melanoma screening in Australians age 50 or older by family practitioners every five years and found a cost of Aust. \$6,853 and Aust. \$11,102 per year of life saved for men and women, respectively. If the screening was performed every other year, the cost per year of life saved was Aust. \$12,137 and Aust. \$20,877 for men and women respectively. Very few details of the model are described and thus the analysis is difficult to critique and no further work from this group has been published on the cost-effectiveness of melanoma screening since this study.

Cristofolini et al¹⁴ in 1992 evaluated the cost-effectiveness of a health education campaign for the early diagnosis of melanoma in Trentino, Italy from 1977-1985. In this study the educational campaign actually saved lives and resulted in savings, though this was not a study on melanoma screening.

The American Academy of Dermatology AAD has sponsored adult skin cancer screenings since 1985, resulting in more than one million screenings⁵⁶. Of those screened, approximately 50,000 possible non-melanoma skin cancers and 10,000 possible melanomas have been discovered. Koh et al⁵⁴⁻⁵⁶ have reviewed two AAD

melanoma screening programs and these will be discussed further when determining parameters to be used in the model. Epstein et al²⁶ 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 al⁵⁵ 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 imply that often a physician or someone other than the individual with a melanoma is often needed to detect earlier-stage melanomas.

Methods

Description of the Model

The model used for the analysis was a decision tree. This model describes two comparable hypothetical populations in 1998, one group screened for melanoma by dermatologists in an outpatient clinic setting by visual inspection of the entire skin of the body and the other group representing the status quo, without a screening intervention. Figures 4.1A depicts the two populations in the model within a tree diagram of events up to a confirmed diagnosis of melanoma and Figure 4.1B continues from there. The unscreened group depicts the usual costs and life expectancies associated with this population for a given prevalence of melanoma. The screened group depicts a comparable population with the same prevalence but with somewhat different costs and life expectancies due to having been screened for melanoma. Melanoma screening if effective, results in the discovery of melanomas with a different and more favorable

distribution of stages due to earlier detection. With a complete model and a determination of all the relevant streams of costs and life expectancies associated with each group, a cost-effectiveness ratio was calculated. We calculated the cost-effectiveness of a “reference case” defined by the Panel on Cost-Effectiveness in Health and Medicine³⁸ as a baseline analysis, which uses a standard set of methodological practices outlined by the panel to improve comparability of cost-effectiveness analyses. Table 4.1 depicts some important model parameters used in the analysis.

Figure 4.1A. Melanoma screening tree.

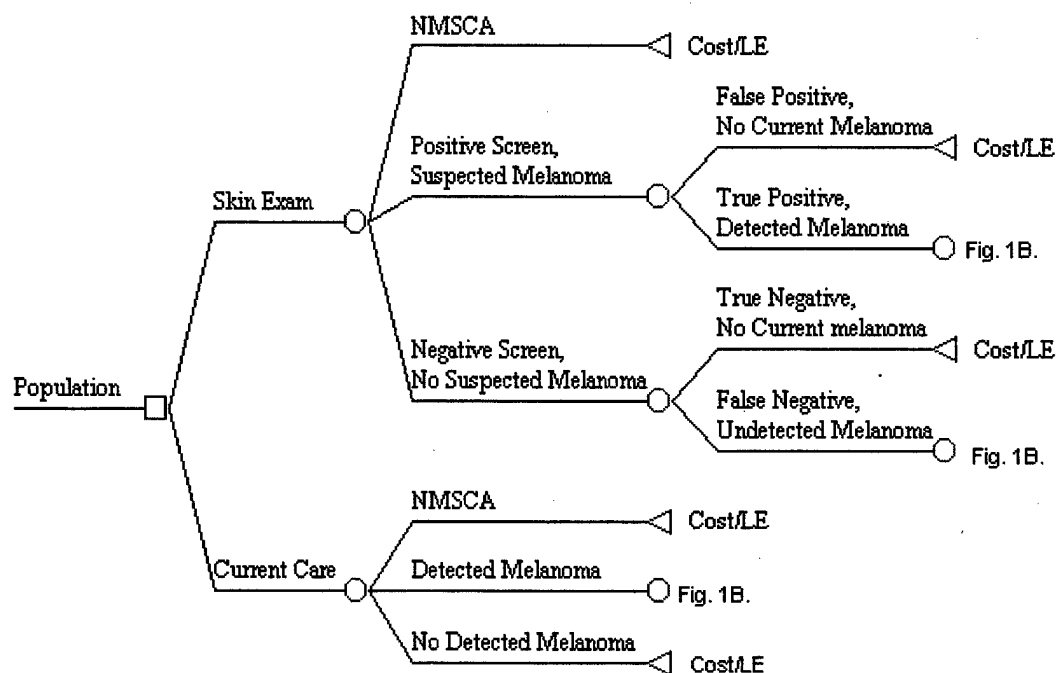


Figure 4.1B. Confirmed melanoma: Melanoma screening tree.

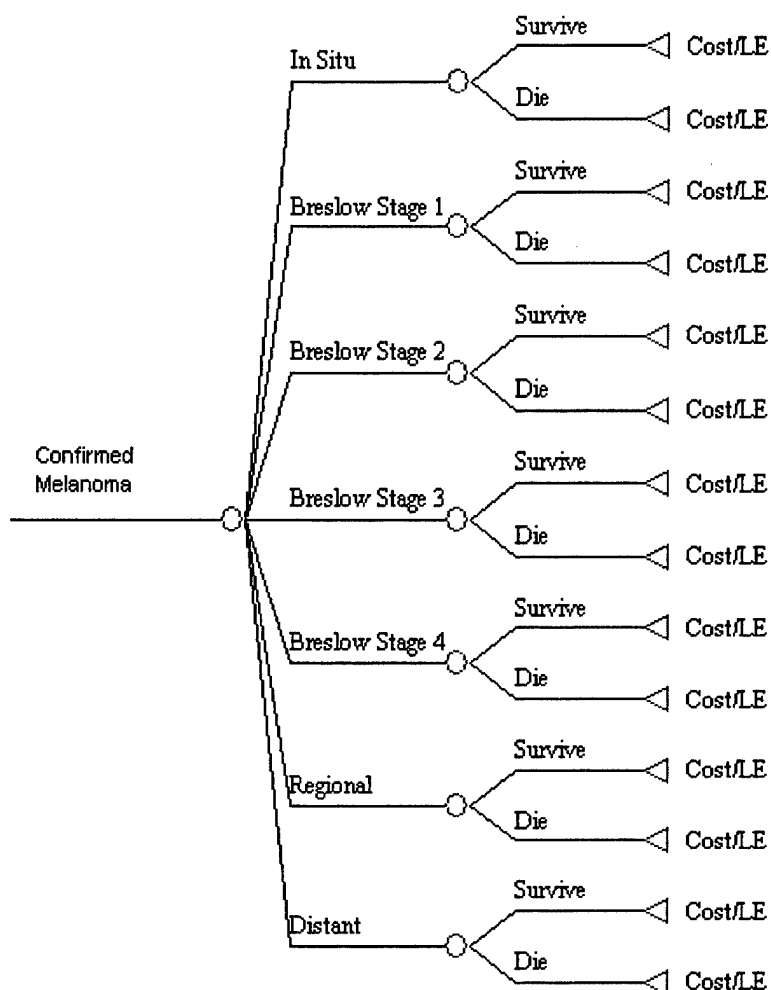


Table 4.1. Model parameters.

<u>Parameter</u>	<u>Value</u>	<u>Reference</u>
Probability positive screen for melanoma	0.016	AAD data ⁵⁶
Sensitivity	0.85	Estimate from AAD data ⁵⁶
Specificity	0.99	Estimate from AAD data ⁵⁶
Prevalence	184 per 100,000	AAD data ⁵⁶ , adjusted to 1997
Probability positive screen for NMSC	0.06	Helfand et al ⁴⁵
Probability true positive, given positive screen for NMSC	0.3	Helfand et al ⁴⁵

Population Estimates

The population for the screened group in the reference case was a high-risk group with a prevalence derived from 1992-94 AAD screenings⁵⁶. When not otherwise specified in this paper a "high-risk population" refers to a self-selected population that would likely choose to take advantage of a voluntary screening similar to the AAD screenings, whose stage distribution of disease has been described^{31,56}. The AAD screened group has been described by Koh et al⁵⁶ and Geller et al³⁶ as adults greater than twenty years old who are at relatively high risk for melanoma, light-skinned people who burn easily and tan poorly or those with a family history of skin cancer, extensive sun exposure, or a higher than average number of nevi. For a comparable unscreened group representing the status quo, we used data on Caucasians in 1998 from the nationally representative SEER database⁸³ age- and gender- matched to the AAD screened population to derive the stage distribution of disease, but attributed to this group the same prevalence of disease as found in the AAD screenings.

The SEER Program is the most authoritative source of information on cancer incidence and survival in the United States and is the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis and survival rates within each stage⁸³. The mortality data reported by SEER are provided by the National Center for Health Statistics. The population covered by SEER is comparable to the general US population with regard to measures of poverty and education, but tends to be somewhat more urban and has a higher proportion of foreign-born persons than the general US population⁸³.

An “average-risk population” in this paper refers to a group whose incidence and prevalence is similar to the population from which the SEER database is derived. Our analysis is of a screening assumed to have taken place in 1998. The incidence of melanoma increased between 1992-94 and 1998. We adjusted the prevalence from the 1992-94 AAD screenings by a factor of 1.21 to approximate the incidence increases between 1992-94 and 1997. We adjusted to 1997 rather than 1998 to account for lead time, which we estimated to be approximately one year. Lead time is discussed further on page 22 under “Effects/Life Expectancy”. The 1992-94 AAD screening prevalence adjusted to 1997 is 6.8 times the incidence in the SEER population in 1998. The prevalence of melanoma in the general population is not known with certainty, thus exactly how much higher-at-risk this screened population is than the age-adjusted general population is not known. If one assumes the prevalence in the AAD group is three times higher than the average U.S. prevalence, which seems reasonable given the description of this population from Geller et al³⁶, then an estimate of the prevalence-to-annual incidence ratio in the general US population would be approximately two³. This implies a preclinical period⁴ for melanoma of about two years. One can use the prevalence-to-incidence ratio to estimate the preclinical period duration as was done by Zelen and Feinlieb⁹⁷ for breast cancer. The length of the preclinical period has significant implications for the ability of screening to be effective, with a short preclinical

³ The formulae for this calculation are: $PIR = P_s / I_s$ and $I_s = I_u * k$, where PIR = the prevalence-to-incidence ratio, P_s and I_s are the prevalence and incidence in screened individuals respectively, I_u is the incidence in unscreened individuals derived from SEER and k is the estimate of the ratio of the prevalence of melanoma in the screened group to an average-risk group (a.k.a. relative risk). In the example given, $P_s / I_u = 6.8$ and $k = 3$ (estimated). Thus, the $PIR = P_s / I_s = 2.27$.

⁴ Defined as the time from when a melanoma is first present and potentially detectable by a skin exam, to the time when it would be discovered without a screening exam.

period making screening less likely to be effective, and a long preclinical period making screening more likely to be effective, *ceteris paribus*. While a long preclinical period makes initial screenings more effective, it also implies that a relatively longer interval between the initial and recurrent screens may be optimal.

In an effort to determine the cost-effectiveness ratio of melanoma screening for populations at different levels of risk, the cost-effectiveness analysis (CEA) was performed using different prevalence rates in the sensitivity analysis.

The age and gender (thirty-nine percent males and sixty-one percent females) distributions of the population were derived from data on the AAD 1992-94 screenings. This gender distribution is comparable to the distribution reported in an AAD screening performed in Massachusetts in 1987⁵⁴. This allowed for a determination of 5- and 10-year age, stage-, and gender-specific survival and life expectancy from SEER databases and life tables.

Effects/Life Expectancy

Life expectancy was the only effect of interest for the cost-effectiveness analysis.

QALYs have not been studied in any depth relating to melanoma in general and thus were not part of the analysis. It is likely that QALYs and YLS are of somewhat similar value for many of those diagnosed and cured from early localized disease with minor surgery alone in non-cosmetic areas, not requiring lymph node dissection. However, for disease requiring chemotherapy, lymph node dissection, or requiring major or

disfiguring surgery, QALYs could be a better measure of effectiveness than YLS alone. Life expectancy gains in the screened arm of the analysis were determined by the improvement in stage distribution of disease with screening (Table 4.2) and thus improvement in probability of survival and life expectancy (Table 4.3A & 4.3B). The stage distribution for the screened group was primarily derived from a report by Koh et al⁵⁶ on AAD screenings from 1992-1994 and further stage delineations were estimated from published data by Balch et al³⁻⁴. The stage distribution for the non-screened group was derived from Caucasians in the 1998 SEER database, age- and gender-matched to the AAD population. An assumption of the model is that detection of melanoma at an earlier stage will result in an improved probability of survival. This assumption is based on the numerous studies showing that stage at time of diagnosis is the best independent predictor of survival³⁻⁴.

Table 4.2. Comparison of stage distribution of melanomas, screened versus non-screened.

	Screened	Non-screened
<u>Stage</u>	<u>AAD</u>	<u>SEER</u>
Melanoma in Situ	0.414	0.364
Localized Breslow Level 1 Thickness	0.352	0.334
Localized Breslow Level 2 Thickness	0.151	0.115
Localized Breslow Level 3 Thickness	0.061	0.075
Localized Breslow Level 4 Thickness	0.011	0.024
Regional Metastases	0.008	0.063
Distant Metastases	0.003	0.026

Table 4.3A. Stage-specific probability of ten-year survival, age-and gender-adjusted*.

<u>Stage</u>	<u>Probability</u>
Melanoma in Situ	Not applicable*
Localized Breslow Level 1 Thickness	86%
Localized Breslow Level 2 Thickness	78%
Localized Breslow Level 3 Thickness	63%
Localized Breslow Level 4 Thickness	59%
Regional Metastases	47%
Distant Metastases	12%

* Derived from analysis of SEER data 1988-1998.

Table 4.3B. Stage-specific life expectancy, age- and gender-adjusted to screening data*.

<u>Stage</u>	<u>Expected value of life years</u>
Melanoma in Situ	30.0
Localized Breslow Level 1 Thickness	28.8
Localized Breslow Level 2 Thickness	26.6
Localized Breslow Level 3 Thickness	22.6
Localized Breslow Level 4 Thickness	20.7
Regional Metastases	17.1
Distant Metastases	4.8

* Derived from analysis of SEER data 1988-1998.

In the model, the expected value of life-years for melanoma patients was based on the stage-specific probability of ten-year survival or death and the life expectancy (LE) given ten-year survival or death.

$$< [p(\text{survival} > 10 \text{ yrs} | \text{stage}) * (LE | \text{survival} > 10 \text{ yrs})] + [p(\text{death} \leq 10 \text{ yrs} | \text{stage}) * LE | \text{death} \leq 10 \text{ yrs}] >$$

Life expectancy was calculated separately for patients in each decade of life for each gender and was stage-specific. We assumed life expectancy for those surviving melanoma ten years (hereafter referred to as melanoma survivors) was the same as cohorts without melanoma, based on an analysis of SEER⁸³ survival data (analysis not shown). Age- and gender-specific life expectancy values for melanoma survivors and those without melanoma came from 1996 National Vital Statistics (NVS) life tables. Life expectancy values for those not surviving melanoma were derived from SEER 1988-98 cumulative databases. The undiscounted life expectancy derived from SEER and NVS was then used to calculate a discounted life expectancy using an approach known as the mixed declining exponential approximation to life expectancy or "mixed DEALE" as described by Keeler and Bell⁵². This formulation allows for increasing chances of dying with age. In contrast, a constant hazard spreads death over too wide a range for all but the severely ill⁵.

The lead time of screening is the difference between the time a patient would seek medical care in the absence of screening and the time that the disease is detected by screening. Lead time bias occurs when not accounting for the fact that screening picks up lesions earlier in time than they would have been diagnosed without screening. Thus, survival from the time of diagnosis is not an appropriate comparison for screened

⁵ The life expectancy for a diseased person using the mixed DEALE is the weighted sum of life expectancies for the original DEALE formula and the fixed lifetime approximation of life expectancy (FLALE). L is life expectancy without disease, d is a constant hazard, and p equals the proportion of the population living exactly L more years (see Keeler and Bell, 1992⁵²).

$$LE = \frac{p(1 - \exp(-dL))}{(d)} + \frac{1-p}{d + (1/L)}$$

and unscreened patients. One method of accounting for lead time is to compare survival for screened patients to lead time plus survival for unscreened patients and this was the method we chose in our analysis. Since melanoma (ten-year) survivors were assumed to have a normal life expectancy, lead time bias was not pertinent to this group. Lead time was pertinent to those dying from melanoma, however. We accounted for lead time by adding an additional 1.14 years to the stage-specific life expectancy of patients who were not screened and died from melanoma. The value for lead time was estimated after deriving the value of the preclinical period as previously described. Average lead time was estimated to be one-half the value of the preclinical period, by assuming that lesions are diagnosed in a random distribution over the preclinical period.

Costs

Weinstein and Stason⁹⁴ have defined the net health care costs in cost-effectiveness analysis as "all direct medical and health care costs [including] costs of hospitalization, physician time, medications, laboratory services, counseling, and other ancillary services." Also included in their definition are costs associated with adverse side effects of treatment, the offsetting costs from savings in health care, rehabilitation and custodial costs due to the prevention or alleviation of disease. Opportunity costs such as the costs of missing work to attend a screening exam were not included in the analysis, since the screen described could be either one of convenience such as in a mall, or a scheduled screen requiring travel time and time off from work. It is controversial whether to include the costs of treating diseases that occur as a result of living longer

because of the intervention^{34,38,94}. Some suggest counting future medical costs associated with living longer because research has shown that analyses that omit future costs are biased in favor of interventions in the elderly that extend life, over interventions that improve quality of life^{34,47,71-72,95}. Costs that arise solely from living longer were not included in the reference case, but a separate analysis was performed on the reference case when such future health costs were included in the total costs and results of both analyses are presented. Future age-specific health costs were derived from two sources, the 1998 Medicare Current Beneficiary Survey⁷⁰ and the 1998 Medical Expenditure Panel Survey⁶⁹. Table 4.4 outlines the costs attributed to each step of the analysis as described below.

Costs in this analysis included the discounted streams of costs related to melanoma screening and melanoma once detected. The cost of the screening exam itself (\$43.46 per screen) was derived from the median salary for dermatologists (\$181,774; 1998 estimate by the Medical Group Management Association, MGMA), the average percentage of clinic costs attributable to the dermatologist's salary (54% by Medicare estimates) and an estimate of the number of screenings that could be performed per year (7717.5; estimate based on a survey of local dermatologists, calculated as five patients per hour, seven hours per day of direct patient care, four and a half days per week, 49 weeks per year). Of note, the estimated number of screens per year is 46% higher than the average number of patients seen per year by dermatologists as reported by the MGMA (5293). However, it is assumed that a screen would take less time than the average dermatologist's clinic visit, which often involves multiple problems, complex

Table 4.4. Costs.

<u>Event</u>	<u>Cost</u>	<u>Reference</u>
Screen	\$43	Estimated
Total biopsy cost	\$206	CMS*
Follow-up visit	\$99	Estimated
Chest X-ray	\$53	Estimated
Laboratory studies (CBC & Comprehensive Panel)	\$71	Estimated
Non-screen dermatologist visit	\$99	CMS*
Screen-detected NMSCA** treatment	\$1,442	Estimated
Non-screen-detected NMSCA** treatment	\$1,580	CMS*
Yearly cost of follow-up visit after detection of NMSCA**	\$99	CMS*
Undiscounted final year of life cost	\$43,443	Hogan et al
Discount rate: Base (Range)	5% (3-7%)	
<u>Stage</u>	<u>Discounted expected value of costs</u>	
Melanoma in Situ	\$13,543	
Localized Breslow Level 1 Thickness	\$15,588	
Localized Breslow Level 2 Thickness	\$17,796	
Localized Breslow Level 3 Thickness	\$23,488	
Localized Breslow Level 4 Thickness	\$25,897	
Regional Metastases	\$67,639	
Distant Metastases	\$43,946	

*Centers for Medicare and Medicaid Services
**Non-melanoma skin cancer

medical decision-making, or procedures. In addition, no biopsies or extensive evaluations would take place during such a screen, nor would prescriptions be written. Had I used the estimated number of patients seen by a dermatologist per year from MGMA (5293), the cost of the screen would have increased to \$63.36. An estimate of the cost of a melanoma screen in an Institute of Medicine funded study¹⁹ on the costs of covering skin cancer screening by Medicare came up with a very similar estimate as the

one used in this study (\$40 per screen) based on a resource-based relative value scale (RVRBS) analysis. The impact of potential differences in the estimated screen cost on the cost-effectiveness estimate is substantial and is discussed in the sensitivity analysis.

The costs for all patients in the screened arm of the model included the cost of the screening examination itself as previously described. Patients with a positive screen incur the costs of a follow-up visit and biopsy with histopathologic processing and evaluation by a dermatopathologist. The costs in the first year of diagnosis for patients with a diagnosis of melanoma in both the screened and non-screened branch of the analysis were based on a report of the stage-specific annual cost of melanoma by Tsao et al⁸⁸. To this amount was added the discounted yearly cost of follow-up based on recent published recommendations for melanoma follow-up¹⁰ for the stage-specific life expectancy. A final-year-of-life cost⁴⁶ appropriately discounted based on life expectancy was also added to the cost calculation for those with melanoma and melanoma in situ. Future costs were age-specific and included in the costs for one analysis referred to previously. All costs were discounted at a rate of three percent and a sensitivity analysis was performed varying the discount rate from zero to five percent.

Screening Exam Parameter Estimates

Screening exam parameter estimates were based primarily on a study of melanoma screening exams by Koh et al⁵⁵ and adjusted to the prevalence of disease used in this study. These screen parameters for the reference case are shown in Table 4.1. A

range of parameters whose values were derived from other studies was tested in the sensitivity analysis.

Cost-Effectiveness

Cost-effectiveness was calculated as the sum of the costs for screening arm less the costs for the non-screening arm, divided by the sum of the life expectancy of the screening arm less the life expectancy of the non-screening arm.

$$\begin{array}{lcl} \text{Cost-Effectiveness} & = & \frac{\Sigma \text{Costs (screen)} - \Sigma \text{Costs (no screen)}}{\Sigma \text{L.E. (screen)} - \Sigma \text{L.E. (no screen)}} \\ \text{Of Screening Program} & & \end{array}$$

Non-melanoma Skin Cancer (NMSCA)

Because non-melanoma skin cancer is much more common than melanoma, melanoma screening exams are likely to find many times more suspected and actual NMSCA than melanomas. A separate analysis was performed adding the costs of screening, evaluating, and treating NMSCA to the reference case. Modeling NMSCA screening requires more assumptions with substantially more uncertainty than in the reference case due to a paucity of adequate data on which to develop the NMSCA model. Unless one chooses to ignore non-melanoma lesions during the screening exam, the impact of evaluating, excluding, and detecting these lesions on the overall costs could be substantial, while the impact on life expectancy is likely negligible. When diagnosed with NMSCA, some form of treatment such as local surgical excision is almost always performed and is the standard of care. One could argue that the value of treating NMSCA is greater to or equal to the cost since it is almost invariably treated once

diagnosed and thus has no negative impact on melanoma screening cost-effectiveness. On the other hand, routine screening for NMSCA in the general population is not currently recommended and screening would certainly be associated with significant costs associated with excluding skin cancer in benign but suspicious lesions detected during the exam. Rarely do NMSCA result in death as attested by the >99% survival in most studies and moreover, early detection is of unknown value. Typically there are cosmetic and functional consequences to NMSCA lesions, which are improved by early treatment of smaller lesions. Thus, including NMSCA screening as part of a melanoma screening program should increase costs without increasing effectiveness (when effectiveness is defined as life years saved as it is in this analysis).

Several assumptions were made in the NMSCA model. First, it was assumed early detection and treatment did not affect life expectancy. This may be overly conservative because it is possible there is some small benefit to life expectancy from screening for NMSCA, but it is almost certainly very small and has never been proven. Thus including improved life expectancy from NMSCA screening did not seem prudent. Second, I assumed NMSCA tumors were detected one year earlier on average with screening than they would have been detected without screening. This is an estimate based on my own professional experience treating patients with NMSCA. The exact accuracy of this estimate has little practical impact on the analysis. I derived the cost for treating NMSCA not detected by screening from a 1993 estimate from The Centers for Medicare and Medicaid Services⁹ (CMS, formerly HCFA,) and adjusted this cost to 1998 values. For NMSCA detected by screening I assumed a cost of 15% less since

the lesion would be smaller in size. This cost would be incurred one year earlier in accordance with the previous assumption. I assumed 6% of screened patients would have a suspected NMSCA based on review of screening for nonmelanoma skin cancer by Helfand et al⁴⁵. Of those with suspected lesions, I assumed 30% had an actual NMSCA while 70% had false positives (i.e. lesions suspected of being NMSCA that resulted in a negative work up based on a review of the available literature^{17-18,48, 60,79}. A cost of \$354 was included for false positives to cover the costs of subsequent biopsy, pathology preparation and reading. Also in the model, patients who developed a NMSCA subsequently incurred a cost of a screening exam each year for their remaining years of life.

Results

Life Expectancy and Survival

In the reference case, individuals with melanoma detected by screening had an 87.8% ten-year survival versus an 83.6% for those not screened. Thus, those screened had a 5.0 percent greater chance of ten-year survival than those not screened. With a prevalence of 186 melanomas per 100,000 people and a sensitivity rate of 84.6%, screening results in an expected benefit of 7.68 lives not lost to melanoma in ten years and an additional eighty-seven life-years per 100,000 patients screened.

Costs

In the reference case, the incremental cost per person was \$42 higher in those screened than in those not screened after all discounted costs and savings resulting

from screening were calculated. The total cost per person screened was \$79 versus \$37 in those not screened. Since the screening exam itself without regard to any subsequent downstream costs or savings was \$43, one can see that: 1) the screening exam cost is a major determinant of the difference in cost per person between those screened and not screened and that, 2) there are some modest net savings in costs per person diagnosed with melanoma if screened.

Cost-Effectiveness

The calculated cost-effectiveness ratios for the screening programs modeled are summarized in Table 4.5. The cost per YLS of melanoma screening in the reference case, a one-time screening of self-selected moderately high-risk men and women, was \$51,481. If the additional induced costs of evaluating and treating non-melanoma skin cancers were included in the analysis, the cost per YLS increased to \$64,646. If future health costs were incorporated into the reference case, the cost per YLS increased from \$51,481 to \$57,639. If the one-time screening program is limited to these same self-selected, high-risk men and women, but only to those aged 50 or older, the cost per YLS was reduced to \$22,368. If the one-time screen in this population was restricted to only women age 50 or older, the cost per YLS was \$30,888, while if limited to men older than age 50, the cost per YLS was \$18,904. A one-time screen in an entire cross section of the Caucasian population at average risk was modeled and the cost-effectiveness ratio was \$172,276⁶.

⁶ This calculation assumed that the prevalence for the "average" Caucasian population was 2.3 times the incidence in Caucasians in SEER data. This estimate was derived by assuming the previously modeled self-selected, moderately high-risk AAD population had a prevalence three times as high as "average", based on published descriptions of risk factors^{36,56}.

Table 4.5. Cost-effectiveness estimates.

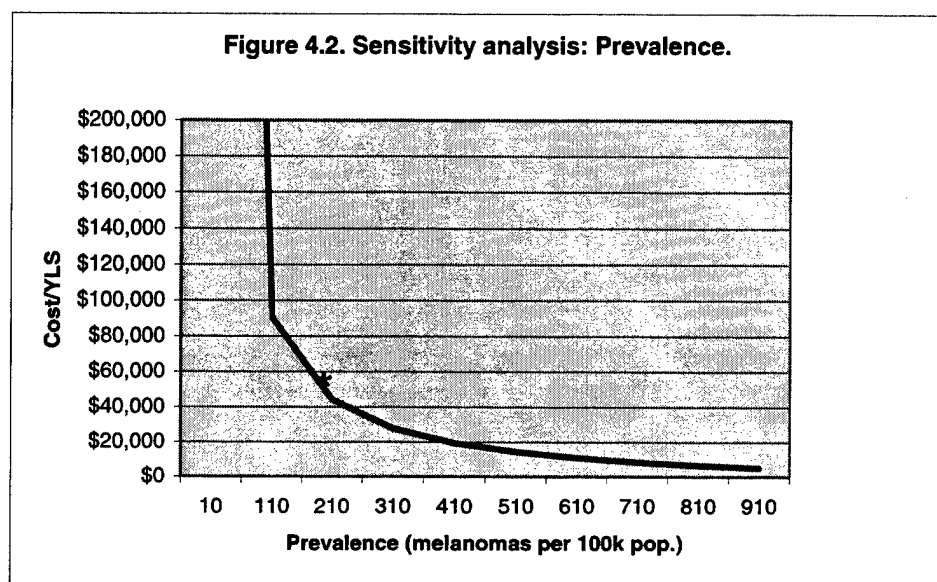
Screen characteristics	Cost per YLS
Reference Case: One-time screen in self-selected (moderately high-risk) population of all ages	\$51,481
One-time screen in self-selected population of all ages including costs for non-melanoma skin cancer	\$64,646
One-time screen in self-selected population of all ages including future health care costs	\$57,639
One-time screen in self-selected, 50+ year old men and women	\$22,368
One-time screen in self-selected, 50+ year old women	\$30,888
One-time screen in self-selected, 50+ year old men	\$18,904
One-time screen in average-risk Caucasian population of all ages	\$172,276

Sensitivity Analysis

Parameters in this decision analysis model were varied over reasonable ranges to determine the robustness of the cost effectiveness estimate and to determine which parameters were the most important determinants in the model.

Prevalence. The prevalence of melanoma in the screened population was varied over a range from 10 per 100,000 people to 910 per 100,000 people. The cost-effectiveness ratio declines exponentially with increasing prevalence over this range (see Figure 4.2). A prevalence of greater than 189 per 100,000 people, yields a cost-effectiveness ratio less than \$50,000. A prevalence of twice that of the reference case (i.e. 376 per

100,000 people) yields a cost-effectiveness ratio of \$21,901 per YLS. As the prevalence of melanoma in the screened population is reduced below 110 per 100,000 people, the cost-effectiveness ratio increases rapidly.



Screen Cost. The cost-effectiveness ratio varied linearly with the screen cost. As a rough rule of thumb the cost-effectiveness ratio is slightly higher than 1000 times the screen cost (see Figure 4.3). A screen cost of \$20 yielded a cost-effectiveness of \$23,015 and a screen cost of \$60 yielded a cost-effectiveness ratio of \$71,558. Thus, in the reference case, each 1000 screens yield approximately one extra year-of-life. Table 4.6 depicts the results of a two-way analysis on the impact of changing the two most important parameters affecting cost-effectiveness, prevalence and the cost of the screen. From \$253,000 to \$713,825 can be seen as bounds on screening the average risk population with recurrent screens annually and \$7,036 to \$29,404 can be seen as bounds on screening a very high-risk population once.

Figure 4.3. Sensitivity analysis: Screen cost.

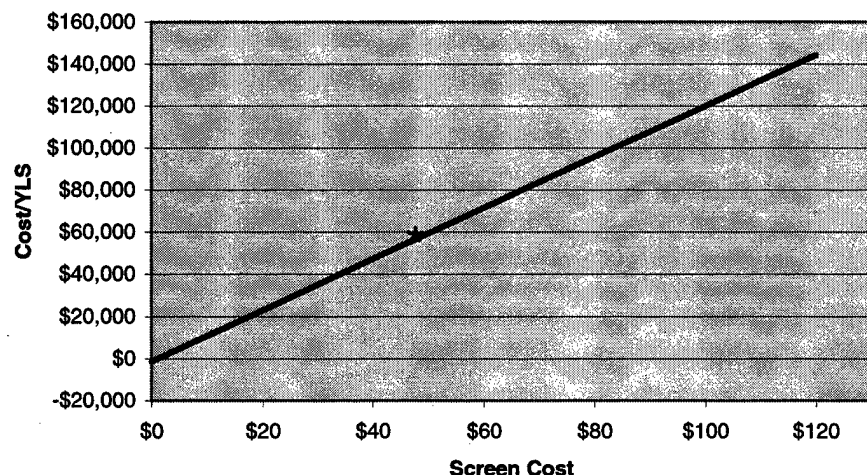
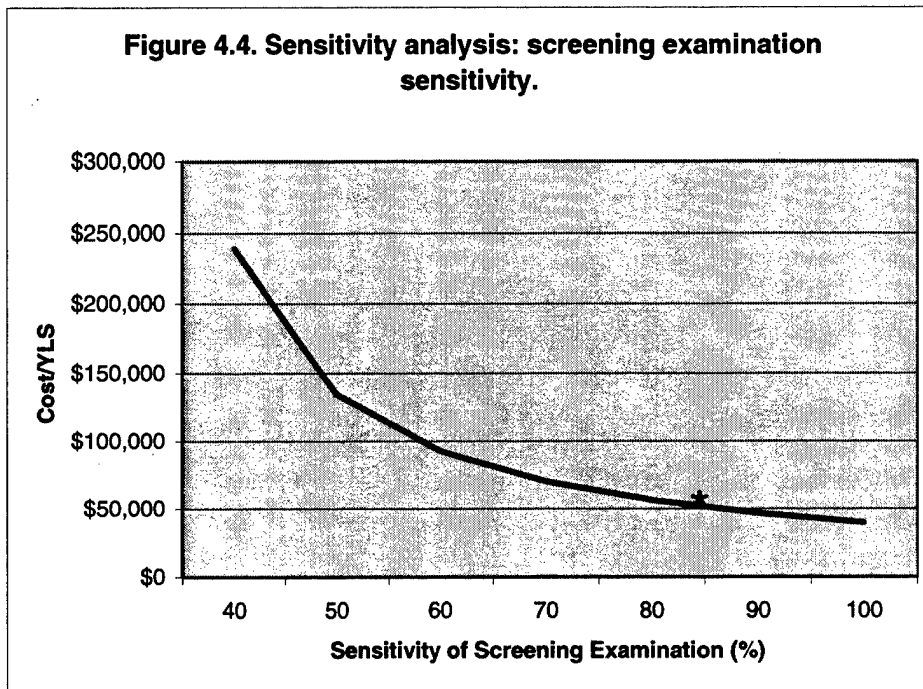


Table 4.6. Two-way analysis of variations in screen cost and prevalence of disease on cost-effectiveness.

Cost/Screen	Prevalence	
	400 melanomas per 100k population	20 melanomas per 100k population
\$20	\$7,036	\$266,465
\$60	\$29,404	\$713,825

Screen Exam Sensitivity. Changes in screen sensitivity alter the cost-effectiveness ratio as depicted in Figure 4.4. The cost-effectiveness of screening remains below \$50,000 in the reference case as long as the sensitivity is greater than or equal to 86%. Figure 4.5 depicts screen sensitivity and screen cost tradeoffs, which yield a constant cost-effectiveness ratio of \$52,000. Over the range of sensitivities evaluated in Figure 4.5, if

every \$8 decrease in cost per screen is associated with a decrease in sensitivity of the examination by less than 10%, the cost-effectiveness will improve. Thus, if a screener other than a dermatologist costs \$35 per screen rather than \$43, and had a sensitivity of better than 75%, the cost-effectiveness would be improved.



Discount Rate. Figure 4.6 shows the effect of changing the discount rate in the analysis of the reference case. The cost-effectiveness ratio ranges from \$20,563 at a 0% discount rate, to \$61,616 at a rate of 7%.

Figure 4.5. Sensitivity analysis: Tradeoff needed between screen sensitivity and cost to keep CEA of \$48,000/YLS.

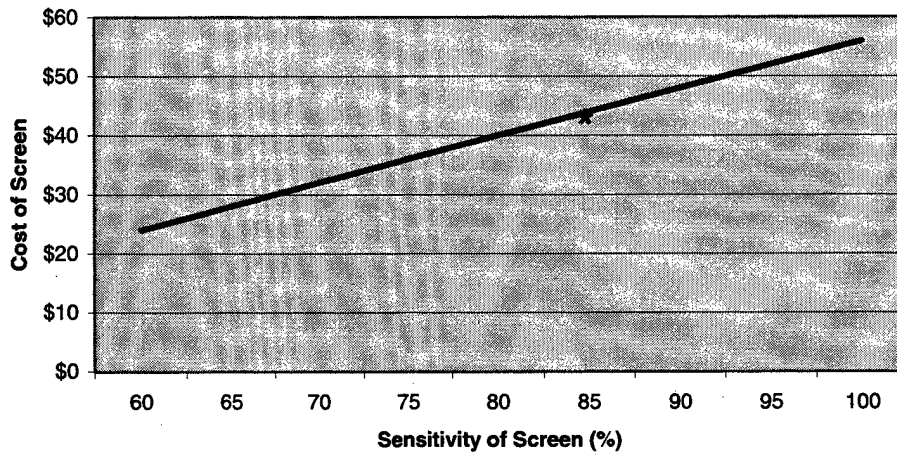
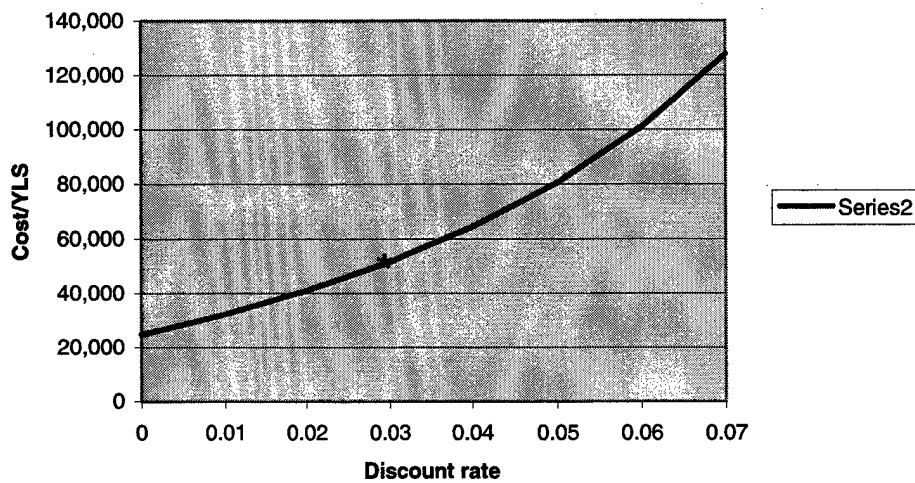


Figure 4.6. Sensitivity analysis: Discount rate.



Discussion

In this decision analysis of melanoma screening, the cost per YLS was \$51,481 in the reference case, a one-time screening for melanoma in a self-selected population by dermatologists. If one includes the costs associated with the screening, detection, and treatment of non-melanoma skin cancer, then the cost of the program was \$64,646 per YLS. These costs are in line with or better than estimates of many cancer screening programs (Table 4.7). According to our estimates, one-time melanoma screening in the setting of the reference case costs approximately the same as screening for cervical cancer with a PAP smear every three years (\$48,000, Eddy²²). It produces more years of life per dollar spent than annual fecal occult blood testing plus sigmoidoscopy every 5 years from age 50 to 85 years⁷ (\$92,900/YLS, Frazier et al³⁰) and more years of life per dollar spent than screening for prostate cancer with a prostate-specific antigen at age 60 (\$158,129/YLS, Krahn et al⁵⁹), but less than biennial mammography for women aged 50 to 79 years (\$16,000/YLS, Lindfors⁶¹, JAMA 1995). These findings are important since melanoma screening programs are not currently routine and opinions on whether screenings should be performed are contradictory. This study suggests that screening of a relatively high-risk population such as described in the reference case will likely save lives and have a cost-effectiveness in line with many other life-saving medical interventions. As should be expected, the estimates of cost-effectiveness of the different screening programs analyzed in this paper differ significantly, from \$18,904 per YLS for a one-time screen of self-selected men age fifty or older to \$172,276 per YLS for a one-time screen in an average-risk Caucasian population of all ages. The range of

⁷ Followed by colonoscopy if either a low- or high-risk polyp was found

estimates corroborates the impressions of many that targeted screening may be warranted and that screening the entire general population would be expensive.

We estimate that a recurrent screen could be performed in the range of three to six years with a reasonably similar cost effectiveness as a one-time screen, based on the previously noted assumptions on prevalence-to-incidence ratios. However, determining the actual cost-effectiveness of recurrent screens and the optimal interval between screenings requires more knowledge of the rate of interval cancers, defined as the rate of cancers developing after a screening.

Table 4.7. Cost-effectiveness estimates of other various cancer screening programs.

<u>Screen</u>	<u>Cost/YLS</u>	<u>Reference</u>	<u>Adjusted from</u>
Prostate-specific antigen, age 60, for prostate cancer	\$158,129	Krahn et al	1996
Annual fecal occult blood testing plus sigmoidoscopy every 5 years from age 50 to 85 years, followed by colonoscopy for low- or high-risk polyp, for colon cancer	\$92,000	Frazier et al	2000
Dermatologist one-time screening of self-selected group for melanoma	\$51,569	Current study	1998
PAP smear every three years for cervical cancer	\$48,139	Eddy	1996
Biennial mammography for women aged 50-79 years, for breast cancer	\$17,193	Lindfors et al	1995

* All estimates converted to 1998 dollars using the Medical CPI, Bureau of Labor Statistics, U.S. Dept. of Labor

If the distribution of prevalence-to-incidence ratios were known or could be estimated from recurrent screens, one could approximate the time in years after a screening when the prevalence of a cancer would return to the pre-screening rate in the absence of further screening. Studies involving computer simulations or a trial of screening with

data on interval cancers collected after screening could provide a better estimate of interval cancers and the prevalence-to-incidence ratios. Such estimates would be useful in determining the most appropriate interval between screens and should be the goal of future research efforts.

The cost-effectiveness estimate in this study is in line with but somewhat higher than that of Freedberg et al who also modeled the use of dermatologists for mass melanoma screening. Freedberg's³¹ cost-effectiveness estimate at a cost of \$30.00 per screen including the effect of NMSCA was \$29,170 per YLS for a one-time screen, versus this study's estimate of \$64,646 per YLS (when we accounted for NMSCA as Freedberg did). Freedberg also used AAD screening data to arrive at the estimate of screening effectiveness. Approximately one-half of the difference in the estimates of cost-effectiveness between Freedberg's estimate and ours can be accounted for by the difference in the estimate of the cost of the initial screening exam. The cost of the initial screening exam was shown in our sensitivity analysis to be a dominating factor on the cost-side of the cost-effectiveness ratio for melanoma screening. Freedberg used \$30 as an estimate of the cost of the initial screening exam, while we used an estimate of \$43. Their estimate of the cost of the screen was based on the charge and cost-to-charge ratio at their university for a physician visit at the time of their study (personal communication, co-author Allan Geller), while our screen cost was calculated from 1998 national estimates of the median annual dermatologist salary, the Medicare overhead rate, and an estimate of the number of screens likely to be performed per year. A recent study sponsored by the Institute of Medicine estimated the cost of screening for

skin cancer to be \$40 per screen based on RBRVS data¹⁹. Had we used the cost of \$30.00 per screen estimated by Freedberg's group, our cost-effectiveness estimate would have decreased to \$48,609 per YLS from \$64,646. We also accounted for lead time and it is not clear if Freedberg did. In addition, we also accounted for improvements in survival from a stepwise improvement in all stages of melanomas including distant and regionally metastatic disease, all four Breslow levels of localized disease, and in situ disease. The rest of the difference cannot be fully explained based on the information known about Freedberg's modeling effort, but these differences are relatively small for a modeling effort such as this. If anything, the similarities between our estimates add credence to these estimates' validity and to the hypothesis that one-time mass melanoma screening is comparably cost-effective relative to many other cancer screening interventions.

Our estimate is substantially higher than that by Grigis et al³⁷ who have also estimated the cost-effectiveness of melanoma screening. However, their model used general practitioners not dermatologists to screen for melanomas in Australia, not the United States, in people over the age of fifty only, and the screen was performed every two to five years rather than just once. They found it cost Aust. \$6,853 to \$20,877 per YLS. Though we did not model a recurrent screen due to a lack of information on interval cancer rates, we found the cost-effectiveness of screening for melanomas by a dermatologist's one-time screen in a moderately high-risk, self-selected group over age fifty was \$22,368 per YLS. For a one-time screen restricted to self-selected men older than fifty, the cost-effective ratio decreased further to \$18,904. Thus, using age-specific

and/or gender-specific criteria for entry into the screening appears to be a simple manner by which one could fairly dramatically reduce the cost-effectiveness ratio of a planned melanoma screening program. With cost-effectiveness ratios of approximately \$50,000 per YLS for a one-time self-selected mass screening and approximately \$20,000 per YLS for a one-time self-selected mass screening of those older than fifty, the cost-effectiveness of these programs fall in line with or are better than many currently funded life-saving medical interventions⁸⁶⁻⁸⁷.

There are several interesting results from the sensitivity analysis, which deserve further review. In the reference case, the screen must be fairly sensitive (greater than or equal to 86%) ceteris paribus, for the cost-effectiveness to remain below \$50,000/YLS. Our estimate of a screen sensitivity of 85% is not unreasonable for a dermatologist, based on the currently available evidence^{31,40,56-57,79-80}. However, a screener with a lower sensitivity could be used while maintaining or lowering the cost-effectiveness ratio if the screen cost was concurrently decreased. Thus, a less sensitive but less costly screener might be a potentially useful strategy for a screening program. A less costly professional such as a highly and specifically trained nurse or nurse practitioner may result in a similar or potentially even more cost-effective melanoma screening or could be used for sequential screening where only select people with a positive nurse/nurse practitioner screen is referred to a dermatologist. Specifically trained nurse practitioners have been reported to have a sensitivity in the range of 67-100%⁷⁵, though such a wide range clearly needs further study. Assuming a sensitivity of 70%, a screen cost of less than \$35 per screen would be more cost-effective than the reference case. Employing

a screener other than a dermatologist would almost certainly be a necessary strategy to consider if one's goal was to provide a screen for a large portion of the population both from a cost-effectiveness standpoint and a practical standpoint. Screening the entire US population would require the full-time efforts of every dermatologist and leave no time for the provision of any other dermatologic services. Recent advances in computer-assisted digital photography and automated pigmented lesion analysis may have implications for melanoma screening and may allow technicians to perform an initial screen, followed by a referral of positive screens. Of course, for melanoma screening, cost-effectiveness is not the only issue. For example, people may be unwilling to settle for an examination that was insensitive, due to the higher number of false negatives that would occur. Part of the benefit of participating in a screening examination is the reassurance the screen provides and an examination with a sensitivity of for instance 70%, may not be adequate to provide such reassurance to the average patient. This study suggests that various issues surrounding screening such as involving other screeners besides dermatologists alone are important to determine and in need of further study.

The sensitivity analysis shows that targeted screening of a high-risk, high-prevalence group of individuals (such as older males or first-degree relatives of family members of melanoma patients) is important to consider for cost-effectiveness. Others have suggested Medicare recipients may be a good target group for melanoma screening programs^{35-36,45}. The majority of Medicare recipients see a physician each year and could easily be screened by the primary care physician or could be referred to a

dermatologist for this purpose. The marginal cost of having the primary care physician or a specially trained nurse/nurse practitioner screening during the primary care visit may be relatively small (an Institute of Medicine study¹⁹ estimate was \$20). In addition to the increased prevalence in older individuals, there appears to be a worse stage distribution of melanomas in older individuals especially men, which suggests screening may be even more effective in this group.

On the other hand, limiting the screening to very high-risk individuals rather than doing population-based screening program, while being more cost-effective, would also lower the total impact of screening on melanoma mortality. If the prevalence of the screened population in the reference case were only 70 per 100,000 people rather than 186 per 100,000 people, the cost would increase to \$146,361 per YLS. Thus, accurate targeting of the population in such a screening program is likely to be quite important, but there remains a tension between targeting to improve cost-effectiveness and mass screening to achieve a greater impact on overall morbidity and mortality.

There are limitations to this study. First, ideally a study on the cost-effectiveness of melanoma screening should be based on prospectively collected data from randomized controlled trial of screening. This is not the case for our study because no such study is available. Thus, for a study such as this, the parameters used come from a variety of different sources and are brought together with the aim of approximating a clinical trial. Clearly, people may have different opinions on what are the appropriate parameters. Moreover, combining parameters from different settings can cause problems if

parameters co-vary with each other. For this reason, we chose to take values for many of the parameters from a single source, the AAD screenings. Thus, the co-varying relationship between these parameters should be valid. In so doing, we increased the internal validity of the results. More credence should be given to the estimate for the reference case than for the scenario of screening the entire average Caucasian population where the prevalence was estimated. Because the patients in the AAD screening were self-selected and at higher-than-average risk, it is possible that they are different than the population from which the SEER data came. It is possible that differences seen in the stage of distribution of melanomas between the screened and unscreened group were due in part to differences in the groups besides screening. However, until a randomized or population-based screening trial is attempted, this problem will be difficult to overcome.

One potential problem not addressed by our study design is that screens in general may be more likely to detect the less aggressive, slower-growing lesions rather than the faster-growing, more aggressive ones. This may happen since slower growing lesions, which tend to be less aggressive by the nature of their slower growth, have a longer window (preclinical period) during which they may be detected. This criticism is lessened by our study design. We controlled for this to a certain degree by the noting the percentages of each stage of the lesions detected in the AAD screenings. The results of the AAD screens suggest that screening does find metastatic lesions and localized lesions of higher Breslow levels, not just thin, non-aggressive lesions.

This study did not evaluate opportunity costs of patients for participating in the screen (e.g. time lost from work, etc...), which could be substantial or minimal depending on how the screen was organized. Exams taking place at places such as malls or at annual primary care provider exams reduce the opportunity costs but select for people who visit those places. This study did not evaluate QALYs. Given the sparse data on QALYs and melanoma, it was felt that such an analysis would not add valuable information to the analysis at this point in time. As shown in this study's sensitivity analysis, a targeted approach to screening may be the best way to ensure a highly cost-effective program. Age, gender, and the general risk of the population to be screened were shown to be important in this analysis. In fact, using age as a criterion for screening may result in an even better cost-effectiveness than estimated here if one accounts for the worsened stage distribution of disease in older individuals, which our analyses did not. The main limitation of targeted screening, using a criterion such as age greater than 50 for entry, is that an age-limited screening design would obviously not affect those outside the screening age and there is in fact, significant morbidity in the U.S. from melanomas in people under age 50. Thus, the main goal of melanoma screening programs should not necessarily be to maximize cost-effectiveness per se. Rather, it may be to minimize melanoma mortality, given certain cost-effectiveness constraints. Further analysis could determine the optimal age, gender, or other risk-stratifying strategy for reducing mortality, given an accepted cost-effectiveness constraint. One could imagine a combined strategy such as doing mass screening of people over a certain age and only screening people under that age who have a given

set of risk factors. In order to determine an optimal strategy, more age- and risk-factor-specific prevalence data is needed.

A one-time screen was used for the reference case because the AAD screenings were for most people (roughly 20%, Geller et al³⁶) a one-time screen. Furthermore, if we had found that a one-time screening had a cost-effectiveness ratio that was too high to be considered worthwhile, a recurrent screen would be even less likely to be worth pursuing. However, melanomas may develop at any age and unlike cervical cancer probably do not have a dramatically long average preclinical stage. Unfortunately, a one-time screen will have a limited impact on the total mortality from melanoma, because one would only have one to six years (estimated) in a person's lifetime during which to detect a preclinical melanoma. Clearly, a one-time screen is most likely not to fall in that window of time for most people and thus, a majority of melanomas would not be detected by such a screening program. A recurrent screen is more likely to have a major impact on morbidity and mortality and will be less cost-effective than (or at best almost equal to) a one-time screen depending on the frequency of the screen and the actual length of the preclinical period for melanomas. Often in public policy decisions however, changes are made and implemented one step at a time and the results analyzed prior to expanding the program (e.g. to involve recurrent screen). Thus, our estimate of the cost effectiveness of an initial melanoma screening provides useful information.

Future studies should focus on developing a screening program that minimizes melanoma mortality while meeting "reasonable" cost-effectiveness constraints. The definition of "reasonable" is best determined by what the cost-effectiveness estimates are for other medical interventions which save lives and in particular cancer screening interventions. Clearly, further analyses should be completed on age and gender-specific recommendations for melanoma screening, the frequency of screens, and the impact on screening recommendations of other risk factors such as family history of melanoma in a first degree relative, numerous nevi, or history of nevi with architectural disorder and atypia.

It will take a clinical trial of screening with good data collection and prospective cost and effectiveness data collected to truly estimate the cost-effectiveness accurately. This study makes a strong case for pursuing such a trial in the near future. A trial such as this would give more accurate data on both the costs and the effectiveness of screening. For instance, it would not require assumptions about the survival of patients with tumors detected by screening being similar to stage-adjusted tumors detected without screening. Rather, the survival for screened and non-screened groups would simply be observed. Assumptions on the cost of the screen would also be avoided by calculating the actual costs as best as possible. It would also provide valuable information on interval cancers and the duration of the preclinical stage. Such a randomized trial should be considered ethical given that the current default standard is not to initiate screening of individuals for melanoma.

Although a melanoma screening program such as the one analyzed here is important, there are also other interventions, which may reduce melanoma mortality and deserve further attention. These include educational campaigns aimed at primary and secondary prevention. Should screening be tied to educational campaigns and should self-screening be taught? These are also important issues deserving of investigation.

In this study, I provide estimates for the effectiveness and cost-effectiveness of a melanoma screening program with and without accounting for the impact of non-melanoma skin cancer. In addition, some age- and gender-specific estimates were determined. Melanoma screening appears effective and relatively cost-effective. The elderly and males appear to be particularly good candidates for screening. These estimates are based on the best evidence-to-date on melanoma screening, but further work is needed to make clear and specific recommendations.

References

1. Aase A and Bentham G. Gender, geography, and socio-economic status in the diffusion of malignant melanoma risk. *Soc Sci Med* 1996;42(12):1621-37.
2. Albert VA, Koh HK, Geller AC, et al. Years of potential life lost: another indicator of the impact of cutaneous malignant melanoma on society. *J Am Acad Dermatol* 1990;23:308-310.
3. Balch CM, Soong SJ, Shaw HM, Urist MM, McCarthy WH. An analysis of prognostic factors in 8500 patients with cutaneous melanoma. In: Balch CM, Houghton AN, Milton GW, Sober AJ, Soong SJ, editors. *Cutaneous melanoma*. Philadelphia: JB Lippincott; 1992. p. 165-87.
4. Balch CM, Cascinelli N, Drzewiecki KT, et al. A comparison of prognostic factors worldwide. In Balch CM, Houghton AN, Milton GW, et al., editors. *Cutaneous melanoma*. Philadelphia: JB Lippincott; 1992. p. 188.
5. Biro I, Price E. Skin cancer. *NY State J Med* 1978;78:753-55.
6. Boer R. From evidence to design support in cancer screening: applications of MISCAN models. Erasmus University, 2000.
7. Bologna JL, Berwick M, Fine JA. Complete follow-up and evaluation of a skin cancer screening in Connecticut. *J Am Acad Dermatol* 1990;23:1098-106.
8. Bystryn JC. An alternate explanation for the increase in the incidence of melanoma being restricted to patients with thin lesions. *Arch Dermatol* 2000;136(7):935-6.
9. The Centers for Medicare and Medicaid Services (CMS, formerly the Health Care Financing Agency). Bureau of Data Management and Strategy, Medicare Decision Support System. Office of Research. 1993.

10. Chartier T and Bigby M. Rational follow-up recommendations for patients with melanoma. *Arch Derm* 2000;136(9): 1145-47.
11. Chen JG, Fleischer AB Jr, Smith ED, Kancler C, Goldman ND, Williford PM, Feldman SR. Cost of nonmelanoma skin cancer treatment in the United States. *Dermatol Surg* 2001;27(12):1035-8.
12. Cochran AJ, Elashoff D, Morton DL, Elashoff R. Individualized prognosis for melanoma patients. *Hum Pathol* 2000;31(3):327-31.
13. Cox DR. Regression models and life tables *J R Stat Soc* 1972;34:187-220.
14. Cristofolini M, Bianchi R, et al. Analysis of the cost-effectiveness ratio of the health campaign... *Cancer* 1993;71 (2):370-4.
15. Dennis LK. Analysis of the melanoma epidemic, both apparent and real... *Arch Derm* 1999;135:275-280.
16. Dennis LK. Increasing risk of melanoma with increasing... *JAMA* 1999;222:1037-38.
17. de Rooj MJ, Rampen FH, Schouten LJ, Neumann HA. Skin cancer screening focusing on melanoma yields more selective attendance. *Arch Dermatol*. 1995;131:422-5.
18. de Rooj MJ, Rampen FH, Schouten LJ, Neumann HA. Factors influencing participation among melanoma screening attenders. *Acta Derm Venereol*. 1997;77:467-70.
19. Dobson A, DaVanzo J, Kerns J. Cost estimates for expanded Medicare benefits: skin cancer screening, medically necessary dental benefits, and immunosuppressive therapy for transplant recipients. Institute of Medicine. 1999
20. Eddy DM, Hasselblad V, McGivney W, and Hendee W. The value of mammography screening in women under age 50 years. *JAMA* 1998;259:1512-9.
21. Eddy, DM. Screening for breast cancer. *Ann Int Med* 1989;111:389-99.
22. Eddy, DM. Screening for cervical cancer. *Ann Int Med* 1990;113:214-226.
23. Edmondson PC, Curley RK, Marsden RA, Robinson D, Allaway SL, Willson CD Screening for malignant melanoma using instant photography. *J Med Screen* 1999;6(1):42-6.
24. Elder DE Skin cancer. Melanoma and other specific nonmelanoma skin cancers. *Cancer* 1995;75(1 Suppl):245-56.
25. Engelberg D, Gallagher RP, Rivers JK. Follow-up and evaluation of skin cancer screening in British Columbia. *J Am Acad Dermatol* 1999;41(1):37-42.
26. Epstein DS, Lange JR, et al. Is physician detection associated with thinner melanomas? *JAMA* 1999;281:640-43.
27. Field SI. Melanoma/skin cancer screening in Michigan. *J Am Acad Dermatol* 1987;16:578-83.
28. Fracheboud J, de Koning HJ, Beemsterboer PM, Boer R, Verbeek AL, Hendriks JH, et al. Interval cancers in the Dutch breast cancer screening programme. *Br J Cancer* 1999;81:912-7.
29. Fracheboud J, de Koning HJ, Beemsterboer PM, Boer R, Hendriks JH, Verbeek AL, et al. Nationwide breast cancer screening in The Netherlands: results of initial and subsequent screening 1990-1995. National Evaluation Team for Breast Cancer Screening. *Int J Cancer* 1998;75:694-8.
30. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA* 2000;284:1954-1961.
31. Freedberg KA, Geller et al. Screening for malignant melanoma: A cost effectiveness analysis. *J Am Acad Dermatol* 1999;41: 738-45.
32. Gallagher RP, Elwood JM , et al. Socioeconomic status, sunlight exposure, and risk of malignant melanoma. *JNCI* 1987;79:647-52.
33. Garbe C, McLeod GR, Buettner PG Time trends of cutaneous melanoma in Queensland, Australia and Central Europe. *Cancer* 2000 ;89(6):1269-78.
34. Garber AM. Advances in cost effectiveness analysis of health care interventions. NBER Working Paper 7198; *National Bureau of Economic Research* June 1999.
35. Geller AC, Miller DR, et al. Cutaneous melanoma mortality among the socioeconomically disadvantaged in Massachusetts. *Am J Pub Hlth* 1996;86:538-44.
36. Geller et al. The First 15 Years of the American Academy of Dermatology Skin Cancer Screening Programs: (1985-1999). *JAAD* in press, 2002.
37. Girgis A, Clarke O, et al. Screening for melanoma by primary health care physicians: a cost-effectiveness analysis. *J Med Screen* 1996;3:47-53.
38. Gold MR, Siegel JE, et al. Cost-effectiveness in health and medicine. 1996. Oxford University Press, New York.

39. Gorey KM, Holowaty EJ et al. Association between socioeconomic status and cancer incidence in Toronto... *Ca Prev Contr* 1998;2: 236-41.
40. Grin CM, Kopf AW, Welkovich B, Bart RS, Levenstein MJ. Accuracy in clinical diagnosis of malignant melanoma. *Arch Dermatol* 1990;126:763-6.
41. Guibert P, Mollat F, Ligen M, Dreno B. Melanoma screening: report of a survey in occupational medicine. *Arch Dermatol* 2000;136(2):199-202.
42. Hagen MD, Garber AM, Goldie SJ, Lafata JE, Mandelblatt J, Meltzer D, Neumann P, Siegel JE, Sox HC, Tsevat J. Does cost-effectiveness analysis make a difference? Lessons from Pap smears. *Med Dec Making* 2001;21(4): 307-23.
43. Hall HI, Miller DR, Rogers JD, Bewerse B. Update on the incidence and mortality from melanoma in the United States. *J Am Acad Dermatol* 1999;40(1):35-42.
44. Harrison RA, Haque et al. Socioeconomic characteristics and melanoma incidence. *Ann Epidemiol* 1998;8(5):327-33.
45. Helfand M, Mahon S, Eden K. Screening for skin cancer. *Am J Prev Med* 2001;20(3 Suppl):47-58.
46. Hogan C, Lunney J, Gabel J, & Lynn J. Medicare beneficiaries' costs of care in the last year of life. *Health Affairs* 2001;20(4):188-95.
47. Johannesson M, Meltzer D, O'Connor RM. Incorporating future costs in medical cost-effectiveness analysis: implications for the cost-effectiveness of the treatment of hypertension. *Med Decis Making* 1997;17(4):382-9.
48. Jonna BP, Delfino RJ, Newman WG, Tope WD. Positive predictive value for presumptive diagnosis of skin cancer and compliance with follow-up among patients attending a community screening program. *Prev Med* 1998;27:611-16.
49. Kafadar K. Simultaneous smoothing and adjusting mortality rates in U.S. counties: melanoma in white females and white males. *Stat Med* 1999;18(23):3167-88.
50. Kanof E. Experience with a skin cancer detection clinic at a state fair. *N Carolina Med J* 1974;35: 159-61.
51. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-481.
52. Keeler E, Bell R. New DEALEs: other approximations of life expectancy. *Med Decis Making* 1992;12(4):307-11.
53. Koh HK, Geller AC, Miller DR, Caruso A, Gage I, Lew RA. Who is being screened for melanoma/skin cancer? Characteristics of persons screened in Massachusetts. *J Am Acad Dermatol* 1991;24:271-277.
54. Koh HK, Caruso A, et al. Evaluation of melanoma/skin cancer screening in Massachusetts: preliminary results. *Cancer* 1990;65:375-79.
55. Koh H, Miller D, et al. Who discovers melanoma? *J Am Acad Derm* 1992;26:914-19.
56. Koh HK, Norton LA, Geller AC, Sun T, Rigel DS, Miller DR, Sikes RG, Vigeland K, Bachenberg EU, Menon PA, Billon SF, Goldberg G, Scarborough DA, Ramsdell WM, Muscarella VA, Lew RA. Evaluation of the American Academy of Dermatology's National Skin Cancer Early Detection and Screening Program. *J Am Acad Dermatol* 1996;34(6):971-8.
57. Kopf A, Mintzis M, Bart R. Diagnostic accuracy in malignant melanoma. *Arch Dermatol* 1975;111: 1291-92.
58. Kosary CL, Ries LAG, Miller BA, Hankey BF, Harras A, Edwards BK. SEER Cancer Statistics Review, 1973-1992. PHS, NIH, Bethesda (MD): NIH Publication No. 96-2789.
59. Krahn MD, Mahoney JE et al. Screening for prostate cancer: a decision analytic view. *JAMA* 1994;272:773-80.
60. Limpert GH. Skin cancer screening: A three-year experience that paid for itself. *J Fam Prac* 1995;40:471-5.
61. Lindfors KK, Rosenquist CJ. The cost-effectiveness of mammographic screening strategies. *JAMA*. 1995;274(11):881-4.
62. Lipsker DM, Hedelin G, Heid E, Grosshans EM, Cribier BJ. Striking increase of thin melanomas contrasts with stable incidence of thick melanomas. *Arch Dermatol* 1999;135(12):1451-6.
63. Loeffel E, Watson W. Screening for skin cancer at a county fair. *Wes J Med*. 1975; 122: 123-26.
64. Long TP. Skin cancer screening in an HMO. *HMO Practice* 1988;2: 84-88.
65. Lynch H, Lynch J, Kraft C. A new approach to cancer screening and education. *Geriatrics* 1973;28: 152-157.

66. Mackie RM and Hole DJ. Incidence and thickness of primary tumors and survival of patients... *BMJ* 1996;313(7057):627-8.
67. Masri GD, Clark WH, et al. Screening and surveillance of patients at high risk for malignant melanoma.... *J Am Acad Derm* 1990;22:1042-1048.
68. McDonald CJ. Status of screening for cancer. *Cancer*.1993;72 (suppl):1066- 70.
69. Medical Expenditure Panel Survey. Agency for Health Care Research and Quality. Rockville, MD; 1998.
70. Medicare Current Beneficiary Survey. Compiled by the Federal Interagency Forum on Aging-Related Statistics. Hyattsville, MD: 1998.
71. Meltzer D. Accounting for future costs in medical cost-effectiveness analysis. *J Health Econ* 1997;16(1):33-64.
72. Meltzer D, Egleston B, Stoffel D, Dasbach E. Effect of future costs on cost-effectiveness of medical interventions among young adults: the example of intensive therapy for type 1 diabetes mellitus. *Med Care* 2000;38(6):679-85.
73. Merrill RM, Capocaccia R, Feuer EJ, Mariotto A. Cancer prevalence estimates based on tumour registry data in the Surveillance, Epidemiology, and End Results (SEER) Program. *Int J Epidemiol* 2000;29(2):197-207.
74. Morton CA, Mackie RM. Clinical accuracy of the diagnosis of cutaneous malignant melanoma. *Br J Dermatol* 1998;138(2):283-7.
75. Oliveria SA, Nehal KS, Christos PJ, Sharma N, Tromberg JS, Halpern AC. Using nurse practitioners for skin cancer screening: a pilot study. *Am J Prev Med* 2001;21(3):214-7.
76. Olsen TGH, Freeser TA, Conte ET, Schroeter AI. Skin cancer screening: A local experience. *J Am Acad Dermatol* 1987;16:637-41.
77. Parker SL, Tony T, Bolden S, Wingo PA. Cancer statistics, 1997. *CA Cancer J Clin* 1997;47:5-27.
78. Piepkorn M, Odland PB. Quality of care in the diagnosis of melanoma and related melanocytic lesions. *Arch Dermatol* 1997;133(11):1393-6.
79. Rampen FH, casparie-van Velsen I, van Huystee B, Kiemeney L, Schouten LJ,. False-negative findings in skin cancer and melanoma screening. *J Am Acad Dermatol* 1995;33:59-63.
80. Rampen RH. Point-counterpoint. Mass population skin cancer screening is not worthwhile. *J Cut Med Surg* 1998;2:128-9.
81. Rigel DS, Friedman R, Kopf A et al. Importance of complete cutaneous examination for the detection of malignant melanoma. *J Am Acad Dermatol* 1986;14:857-60.
82. Roetzheim RG, Tenant C et al. Effects of insurance and race on early detection of cancers. *JNCI* 1999;18;91(16):1409-15.
83. Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-1999), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2001, based on the November 2000 submission.
84. Sonnenberg A, Delco F, Inadomi JM. Cost-effectiveness of colonoscopy in screening for colorectal cancer. *Ann Intern Med* 2000;133:573-584.
85. Swerlick RA, Chen S. The melanoma epidemic. Is increased surveillance the solution or the problem? *Arch Dermatol* 1996;132(8):881-4.
86. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care* 2000;38(6):583-637.
87. Tengs TO, Adams ME, Pliskin JS, Safran DG, Siegel JE, Weinstein MC, Graham JD. Five-hundred life-saving interventions and their cost-effectiveness. *Risk Anal* 1995;15(3):369-90.
88. Tsao H, Rogers GS, et al. An estimate of the annual direct cost of treating cutaneous melanoma. *J Am Acad Derm* 1998;38:669-80.
89. Tucker MA, Fraser MC, et al. Risk of melanoma and other cancers in melanoma-prone families. *J Invest Derm* 1993;100:350S-355S.
90. U.S. Census Bureau. Statistical abstract of the United States: Census 2000
91. Vaseen HFA, Bergman W, et al. The familial dysplastic nevus syndrome: natural history and the impact of screening... *Eur J Ca Clin Onc* 1989;25:337-341.
92. Van Durme DJ, Ferrante JM et al. Demographic predictors of melanoma stage at diagnosis. *Arch Fam Med* ;2000;9:606-11.

93. Weary P. A 2-year experience with a series of rural skin and oral cancer detection clinics *JAMA* 1971;217:1862-63.
94. Weinstein MC and Stason WB. Foundations of cost-effectiveness analysis for health and medical practices *NEJM* 1977;276:716-21.
95. Weinstein MC and Manning WG. Theoretical Issues in cost-effectiveness analysis. *J Health Econ* 1997;16:121-28.
96. Zagula-Mally Z, Rosenberg E, Kashgarian M. Frequency of skin cancer and solar keratoses in a rural southern county as determined by a population sampling. *Cancer* 1974; 34: 345-49.
97. Feinleib M, Zelen M. Some pitfalls in the evaluation of screening programs. *Arch Environ Health* 1969;19(3):412-5.

CONCLUSION

Melanoma is a serious public health concern in the United States and recent decades have seen alarming increases in its incidence and resulting mortality. Screening for melanoma is thought by many to be an effective way to detect the malignancy at an earlier and more favorable stage and thus reduce the mortality from this disease. In fact, this is assumed in the practice of dermatology today. However, recommendations for or against melanoma screening by cancer societies and preventive health care organizations are mixed. Given the scope of the melanoma problem it is surprising that few studies are available to help guide such screening recommendations. In the absence of solid research, it is understandable why the public health messages being sent are mixed. This is in sharp contrast to many other cancers such as those of the breast, cervix, colon, and prostate where much more research on both effectiveness and cost-effectiveness of screening interventions is available. Unfortunately, mixed public health messages may discourage people in need of screening and encourage screening among those who do not need screening. However, until better research is available on melanoma screening it will be impossible to achieve a rational approach to screening or a consensus on recommendations.

The primary focus of this dissertation has been to examine the effectiveness and cost-effectiveness of screening for melanoma. As part of this process, several previously

unanalyzed or minimally analyzed aspects of melanoma epidemiology have been investigated including differences in melanoma incidence and survival due to stage at diagnosis, decade of life, and gender of the patient. Though there were no prospective, randomized controlled clinical trials, data were available in the form of implemented screening programs initiated by the American Academy of Dermatology. Using these data and data from SEER and other cancer registries, a decision analysis was used to simulate a clinical trial of melanoma screening. The results of these analyses should be seen as attempting to use the best available data to estimate cost-effectiveness and suggest factors impacting such screening programs.

Our decision analysis can help to determine the value of performing an actual trial of melanoma screening. It is interesting to speculate on the value of obtaining better information on the effectiveness and cost-effectiveness of melanoma screening by funding a clinical trial of screening. The value of a definitive, successful screening trial could be determined by estimating the changes in practice that would occur if various guidelines for screening were implemented after such a study. Suppose screening was not cost-effective for a percentage of the population, but was cost-effective for another group of the population. First, one could assume a certain screening criterion might be implemented based on that information. Then, one could determine how many people are currently being screened inappropriately and appropriately, given this assumed criterion. Thus, one could estimate what resources are currently being used inappropriately on screening those people not meeting the criterion and what resources are being lost by not screening those people who do meet the assumed criterion.

Estimating the value currently lost by not screening appropriate individuals is more difficult and would most likely involve setting a monetary value for a year-of-life-saved. For instance, if one assumed that every year-of-life-saved is valued at \$100,000, and also assumed screening costs \$50,000 per year-of-life-saved for the appropriately screened group, then a value could be arrived at for the amount currently being lost by current screening practices. Thus, the value of obtaining better information on screening for melanoma, depends on what screening criterion is likely to be found in a melanoma screening study as well as the current practices. Additionally, one might include how likely it is that a study would actually change the current practices of screening, since recommendations for screening are not always practiced, even once made. The results of this thesis aid in determining what criteria are likely to be recommended after such a study. Hypothetically, if the result of a melanoma screening study suggested 20% of the population that is not currently screened should be screened every three years, the value of performing such a trial would likely be very high given a few reasonable assumptions and the trial would likely pay for itself after only a few screenings⁸. This "back-of-the-envelope" calculation though obviously limited, suggests that a trial of melanoma screening if funded may well pay for itself in relatively short order.

⁸ Assume 20% of the US population is screened every three years and the prevalence of melanoma in this group is 200 per 100,000 population. Further assume each screening of a melanoma patient results in 0.5 years of life saved (YLS) and costs \$50,000 per YLS and that each YLS is worth \$100,000 (appropriately discounted). Then, each round of US screening would result in a savings of approximately \$12.5 million without accounting for additional savings from not screening those currently being screened inappropriately. Elwood² in 1994 estimated a screening trial for melanoma would cost approximately \$11 million for a study with several years of follow up. Even if this estimate of the cost of a trial is doubled to \$22 million one can see that a trial would likely pay for itself after two screenings, more or less.

The results of these analyses could also be used to help design a study of melanoma screening by helping to determine which groups to target in an initial study. Often, first screening trials are performed on high-risk individuals with the belief that if screening this population were not particularly cost-effective, that screening an even less at-risk population would certainly not be as cost-effective or worth investigating. Such a study would yield initial results at less cost than screening of the general population. These analyses suggest that using age and possibly gender would be an easy way of targeting a higher risk population with a lower study cost and a more favorable cost-effectiveness ratio than the general population. Another way to enroll higher than average risk individuals would be to have people self-select themselves for screening as was done in the AAD screening programs. By "self-select" in this context I am referring to a screening program that is set up and advertised, possibly takes place in a public arena such as a shopping mall, and in which people passing by or seeing the ads then self-select themselves for screening. It appears from the results in this thesis that a combination approach of self-selection and age-specific criteria could be used to achieve a lower cost-effectiveness ratio than screening the general population. In the results presented here, the screening of a self-selected group of men and women 50 years or older was more than five times more cost-effective than screening the general population.

Future Directions

Screening as evaluated in this thesis only considered dermatologists performing the screen; however, screening for melanoma need not be so narrowly defined. Significant

improvements in melanoma screening might be accomplished by having non-dermatologists perform screenings in parallel or serially with dermatologists. For instance, these results showed that the cost of the initial screening examination is the primary determinant of the total costs of the program. Table 5.1 shows the range of C-E ratios from the cost-effectiveness analysis if the screen cost is varied from \$20-\$60. One can see that the screen cost has a significant impact on these estimates. The simplest way to reduce the screen cost would be to have a less-expensive person performing the screen such a nurse or nurse practitioner. Our results also showed that this less expensive screener could have a significantly lower sensitivity while still maintaining or reducing the cost-effectiveness ratio (see Figure 4.5). One screening strategy would be to have professionals other than dermatologists perform an initial screening exam and either perform necessary biopsies or refer all positives screens to a dermatologist for further evaluation. These non-dermatologist professionals would preferably be highly trained for screening exams to enhance accuracy. It is possible that such professionals could achieve a sensitivity equal to or even greater that of many dermatologists without any decrease in specificity of the examination.

Another way to decrease costs would be to have general practitioners perform the examination as part of an annual visit. This would decrease the marginal cost of such a screening examination and also reduce the patients' opportunity costs, since they would presumably already be visiting the physician for other reasons. The problem with this strategy is that primary care physicians already are burdened with performing so many tasks that it simply may not be practical to add more while maintaining the accuracy of

Table 5.1. Range of cost-effectiveness estimates, varying screen cost from \$20-\$60.

Screen Scenario	Screen cost \$43	Screen cost \$20-\$60
Reference Case	\$51,481	\$23,015 - \$71,558
Ref Case + NMSCA	\$64,646	\$36,692 - \$84,361
50+ year old men and women	\$22,368	\$7,227- \$33,045
50+ year old women	\$30,888	\$11,981- \$44,223
50+ year old men	\$18,904	\$4,394- \$29,136
All Caucasians	\$172,276	\$84,633- \$234,089

the screening examination. Also, such a strategy would only include screening of people who visit their primary care physician. Another way to decrease opportunity costs of the patient is to have the screens take place at points of convenience such as malls, and this is done in practice in many screenings. Another type of screening protocol that could be performed involves the addition of recent technology for screening pigmented lesions such as digital epiluminescent microscopy (DEM), which can be performed by a technician and the results can be interpreted later by a dermatologist or immediately by a computer program. We have recently completed a pilot study of such a computer-assisted digital epiluminescent microscopy (CADEM) and preliminary results show CADEM has an accuracy approximately equal to that of dermatologists. Other studies have found DEM when performed interpreted by dermatologists to improve the accuracy of their evaluation of pigmented lesions. If CADEM was shown to be accurate, technicians could be trained to screen all or most pigmented lesions on patients and only those with positive screens would be referred to a dermatologist for further evaluation and likely biopsy. Such a program might be ideal for screening if one's goal was to screen a significant proportion of the population and

maintain a low cost-effectiveness ratio. In fact, it turns out that the number of practicing dermatologists precludes their screening the entire US population each year, even if all dermatologists spent all their time screening for melanoma and did no other work.

Research on melanoma screening is lacking and much is needed in order to make informed decisions on how best to reduce the mortality from this disease. Recently, a research group has started a randomized trial of a community-based population screening for melanoma in Queensland, Australia ¹. Forty-four communities with a population 560,000 adults aged 30 years or more will be randomized to receive either a community-based screening program for 3 years or normal practice. The screening program involves whole body skin examination by a physician, provides open access to skin cancer screening clinics, and promotes thorough skin self-examination with many years of follow-up. This trial should provide not only a great deal of information on screening for melanoma but also because recurrent screens will be performed, it should provide data on the natural history of melanoma. Because medical practices and costs are different in the US and Australia and there is greater heterogeneity of the US population and environment, an argument for such a trial in this country in the near future can be made. If such a trial is not performed it is likely that decisions regarding screening will be made based on a person's socioeconomic or educational level, the patterns of referral of an individual's primary care physician, practice patterns of an individual's insurance carrier, or simply personal preferences regarding health care. Such determinants of whether an individual is screened for melanoma do not necessarily maximize public welfare or correlate well with cost-effectiveness. Further

work is needed on the impact of targeting screening. The development of a "risk score" for melanoma could help individuals determine their risk of melanoma and guidelines for screening could be made based on such risk scores. Such a risk score might logically include skin type and ability to tan, environmental exposures, family history of melanoma, personal history of melanoma and other skin cancers, and in the future possibly even genetic markers. It is important to remember that while targeted screening does lower the cost-effectiveness ratio, highly-targeted screening programs can result in a significant number of people with melanoma not being screened.

A logical and consistent approach to melanoma screening will only be achieved after the necessary foundation of research has been performed. Such research appears clearly warranted based on the results presented here.

References

1. Aitken JF, Elwood JM, Lowe JB, Firman DW, Balanda KP, Ring IT. A randomised trial of population screening for melanoma. *J Med Screen* 2002;9(1):33-7.
2. Elwood JM. Screening for melanoma and options for its evaluation *J Med Screen* 1994;1(1):22-38.