GENDER, AGE, AND SCREENING DIFFERENCES IN INDIVIDUALS DIAGNOSED WITH MALIGNANT MELANOMA IN THE UNITED STATES

By LISA E. PADDOCK, MPH

A dissertation submitted to the School of Public Health

University of Medicine and Dentistry of New Jersey

and the Graduate School – New Brunswick

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

for the degree of Doctor of Philosophy

UMDNJ-School of Public Health

Awarded jointly by these institutions and written under the direction of

Professor George G. Rhoads, MD, MPH

And approved by

_____

_____

_____

_____

Piscataway/New Brunswick, New Jersey October, 2012

ABSTRACT OF THE DISSERTATION

GENDER, AGE, AND SCREENING DIFFERENCES IN INDIVIDUALS DIAGNOSED WITH MALIGNANT MELANOMA IN THE UNITED STATES

By Lisa E. Paddock, MPH

Dissertation Director:

George G. Rhoads, MD, MPH

Melanoma is the rarest but most lethal form of skin cancer. This dissertation focuses on three salient issues in melanoma research –pediatric incidence, completeness of ascertainment in cancer registries, and the role of screening. Chapter 1 addresses melanoma incidence in children in whom 40-60% of melanoma cases may be initially misdiagnosed. The purpose was to examine differences between children/adolescents and adults in demographics and clinical characteristics of melanoma. Cases diagnosed from 1995-2008 were identified using the Cancer in North America (CINA) Deluxe database from the North American Association of Central Cancer Registries (NAACCR). Frequency distributions and incidence rates were tested for differences using chi square statistics, rate ratios, and annual percent change. Results show that children were diagnosed at later stages (x^2 = 63.59; p<.0001) and were more likely to have thicker

lesions (x^2 = 22.3; p<0.0001) than adults. Questions are raised about the role of hormonal/reproductive factors contributing to age and gender differences. Because of the growing evidence for under-reporting of melanoma incidence we investigated this issue in New Jersey (Chapter 2). We surveyed dermatologists to identify why melanoma may be underestimated and to quantify the extent of reporting delay. We also estimated the missing melanoma cases using a capture-recapture analysis. Using log-linear models we approximated that 817 melanoma cases were missed annually, most likely from physicians and pathology labs. These estimates can be used to improve the accuracy of melanoma incidence rates and to make targeted adjustments for reporting. In Chapter 3 we examined long term melanoma survival rates for skin self-examiners (SSE), which is a useful and inexpensive screening method that has the potential to reduce the risk of advanced disease. Cases were diagnosed in 1987-1989, followed through 2007, and analyzed using competing risks (CR) analysis. Cumulative incidence functions and proportional hazards regression models were fitted. The cumulative incidence curves by SSE were not statistically different (p=0.32) for death due to melanoma in the presence of CR. Skin awareness (HR= 0.49, p=0.002) was associated negatively and thickness (HR= 1.21, p<0.001) was associated positively with melanoma death. Although we did not find a significant association between melanoma mortality and SSE, we have confirmed previous findings of a protective association with skin awareness.

ACKNOWLEDGEMENTS

Always bear in mind that your own resolution to succeed, is more important than any other one thing."

— Abraham Lincoln
November 5, 1855

I am very grateful to my committee members, without whom this research would not be possible. I would like to thank Dr. George Rhoads, my advisor, for many hours of thoughtful discussion and insight. I appreciate the guidance that you have provided me, Dr. Rhoads. Thank you also to Dr. Shou En Lu, who was my teacher for my first survival analysis class and my statistics mentor during this dissertation. Dr. Lu, your advice has always been straightforward and meaningful – two very important characteristics for a student. I would also like to recognize Dr. Elisa Bandera, your endless encouragement gave me the incentive that I needed to continue pursuing my degree even when the thought of completion was distant. I have also learned volumes from our ovarian cancer study collaborations, particularly the day-to-day tasks necessary to take an epidemiologic research project from development to publication. I am especially indebted to Dr. Berwick for her extensive research in melanoma and for her collection of the skin self-examination data in 1988-89. Dr. Berwick, your copious notes provided me with a glimpse of how the people in your study discovered their melanoma lesions and their individual stories of treatment and survival. Your thoughtful criticism has challenged me to think beyond the published statistics.

I always joke that when my parents told me to climb on the school bus to go to Kindergarten I had no idea that it would be 30 years until school was over. Undoubtedly, my academic career would not have happened without the positive reinforcement from my parents. There was never any goal too lofty or hurdle too high that you didn't encourage me to tackle. Mom and Dad, I owe this achievement to you.

Since the dissertation is the pinnacle of academic training, it was fitting that I was preparing for my defense during Olympics 2012. Of course behind every good athlete (even an academic athlete!) is a great cheerleader. My husband, John, has been my constant rock and has been on the sidelines cheering for the duration. There was never a question of *if* or *when* I would finish, just constant encouragement. I cannot even express my gratitude to my children, Jack and Brooke, who never complained – not even once - that my degree was higher on the priority list than dinner and playtime. Special thanks to my sisters, family, and friends who offered support while I was studying.

I couldn't have met this challenge if I didn't know all of you. ~

Table of Contents

Preliminary Sections

Abstract of the Dissertation ii
Acknowledgements iv
List of Tables viii
List of Figures x

Introduction 1
Melanoma Etiology 1
Incidence 4
Mortality 7
Risk Factors 8
Prevention, Screening, and Early Detection 12
Survival 14
Summary 15
References 17

Chapter 1 Melanoma Incidence in Children and Adolescents in the United States, 1995-2008 29
Abstract 29
Background 31
Methods 33
Results 38
Discussion 43
Conclusion 48
References 66

Chapter 2 : Under-Reporting and Reporting Delay for Melanoma Incidence in New Jersey 69
Abstract 69
Background 70
Methods 74
Part One: Survey of Dermatologists 74
Part Two: Reporting Delay 77
Part Three: Capture – Recapture Estimation 78
Results 80
Part One: Survey of Dermatologists 80
Part Two: Reporting Delay 82
Part Three: Capture – Recapture Estimation 84
Discussion 85
Conclusion 92
References 99

Chapter 3 Skin Self-Examination and Long-Term Melanoma Survival 101
Abstract 101
Background 102
Methods 105
Results 109
Cumulative Incidence Estimates – Overall Survival 110
Cumulative Incidence Estimates – Skin Self-Examinations (SSE) 110
Competing Risks Regression 111
Discussion 115
References 127
Appendix 3-1: Development of indices used in analysis 130
Comorbidities Index 130
Screening Index 134

Concluding Remarks 136

Curriculum Vitae 140

LIST OF TABLES

Table 1 -1: Population-based Studies for Childhood Melanoma 49

Table 1-2: Melanoma Incidence in Children and Adolescents by Gender and Anatomic Site, 1995-2008 50

Table 1-3: Melanoma Incidence by Race/Ethnicity and Age, 2003-2008 51

Table 1-4: Melanoma Incidence by Gender, Stage, and 10-year Age Groups, 2003-2008 52

Table 1-5: Melanoma Incidence in Children & Adolescents Compared to Adults by Breslow Depth, 20-year Age Groups, 2004-2008 53

Table 1-6: Melanoma Incidence for Children & Adolescents Compared to Adults for Histologic Subtype, 2003-2008 54

Table 1-7: Melanoma Incidence in Children & Adolescents Compared with Adults by 5-year Age Group and Gender, 1999-2008 55

Table 1-8: Melanoma Incidence in Children & Adolescents Compared to Adults by Race, Ethnicity, and Gender, 2003-2008 56

Table 1-9: Annual Percent Changes (APC) in Melanoma Incidence for Children & Adolescents Compared to Adults by Gender, 1999-2008 57

Table 2-1: Studies Addressing Melanoma Underestimation, Reporting Delay and Reporting Error 93

Table 2-2: Reporting Patterns for Incident Melanoma Cases to the NJSCR 94

Table 2-3 : Reporting Delay For Melanoma Cases Diagnosed Between 1995 and 2003 and Followed For Five Years by First Reporting Source 95

Table 2-4: Three-Source Capture-Recapture Schema 95

Table 2-5: Unique Combinations of Sources Identifying Melanoma Cases in 2008..... 96

Table 2-6: Total Number of Melanoma Cases Based on Log-Linear Models of Multiple Reporting Sources in New Jersey, 2008..... 96

Table 2-7: Predicted Values of Melanoma Cases by Reporting Source Using the Preferred Log-Linear Fitted Model..... 97

Table 3-1: Comparison of Skin Self-Examiners (SSE) and Non-Skin Self-Examiners (no SSE) by Patient Characteristics 121

Table 3-2: Cumulative Melanoma Mortality Rates Adjusted For Competing Risks Stratified by Skin Self-Examination (SSE) Status..... 122

Table 3-3: Cumulative Melanoma Mortality Rates Adjusted For Competing Risks Stratified by Type of Skin Exam, Long Term Follow-Up..... 123

Table 3-4: Univariate Analysis of Select Factors Associated with Melanoma Death, Competing Risks Regression 124

Table 3-5: Multivariate Analysis of Factors* Associated with Melanoma Death, Competing Risks Regression 125

Table 3-6 (Appendix): Weights Used for Comorbid Conditions Based on Charlson Weighted Index of Comorbidity..... 132

Table 3-7 (Appendix): Frequency Distribution of Comorbidity Scores..... 133

Table 3-8 (Appendix): High and Low Screening Cutoffs by Screening Type 135

LIST OF FIGURES

Figure 0 -1: Melanoma Incidence and Mortality in the U.S., 1973-2009 16

Figure 1-1: Relative Frequency Distributions of Melanoma Diagnosed in Children, Adolescents, and Adults by Anatomic Site, and Gender, 1995-2008 58

Figure 1-2 Melanoma Incidence Rates by Race & Ethnicity and 10-Year Age Groups, 2003-2008 59

Figure 1-3: Relative Frequency Distribution of Melanoma Diagnosed by Race and Ethnicity, Children/Adolescents (age 0-19) Compared to Adults (20+), 2003-2008 60

Figure 1-4: Relative Frequency Distribution of Melanoma by Breslow Depth (mm) and Age Group 2004-2008 61

Figure 1-5: Relative Frequency Distributions of Melanoma by Stage at Diagnosis for Children (age≤9), Adolescents (age 10-19), and Adults(age 20+), 2003-2008 62

Figure 1-6: Relative Frequency Distributions of Melanoma in Children/Adolescents (age 0-19) Compared to Adults (age 20+) by Distribution of Histologic Subtypes, 2003-2008 63

Figure 1-7: Melanoma Incidence Rates by Gender and 5-year Age Group, 1999-2008 64

Figure 1-8: Melanoma Incidence Rate Ratios (Female:Male) by 5-year Age Group, 1999-2008 65

Figure 2-1: Primary Sources of Melanoma Cases Submitted the NJSCR for the 2008 Diagnosis Year 98

Figure 3-1: Estimated Cumulative Incidence Curves with Melanoma Death and Other Causes of Death as Competing Events for Skin Self-Examiners (SSE) and Non-Skin Examiners (no SSE).. 126

INTRODUCTION

Melanoma of the skin, or cutaneous malignant melanoma (hereafter referred to as 'melanoma'), is the rarest but most lethal form of skin cancer. Other common forms of skin cancer, basal cell and squamous cell, are more prevalent but not as deadly.[1] Although the first English language report of melanoma was made by Dr. William Norris in 1817[2], describing a familial occurrence of melanoma in a man and his father, much still remains unknown about melanoma. This chapter will provide a brief background of melanoma for my dissertation which focuses on age, gender, reporting, and screening differences.

MELANOMA ETIOLOGY

Melanocytes are cells in the skin that produce melanin, giving skin its pigmentation. Melanocytes become more active when exposed to ultraviolet light, thereby creating more melanin and causing the skin to tan. Clusters of melanocytes and surrounding tissue may form noncancerous (benign) growths called moles or nevi. These nevi can develop into melanoma, which may or may not have metastatic competence.[3-5] The etiology of melanoma is not completely understood[6] and several mechanisms for origin have been proposed.[1,7] Whiteman et al. suggested two pathologic pathways to

melanoma. The first pathway, melanocyte proliferation, requires little if any sun exposure and mainly gives rise to melanocytes on the trunk in nevus-prone individuals. The second pathway, the chronic exposure model, requires ongoing exposure to UV light to drive the development of melanoma, which usually occurs at older ages and is associated with other skin diseases.[8,9] Armstrong proposes that there are three pathways linking a normal melanocyte to melanoma: (1) via a melanocytic nevus cell, (2) via a melanocytic nevi, or (3) by some other undefined mode.[10] For paths one and two, nevus cells are mutations thought to be triggered by exposure to UV radiation in a susceptible host. This model suggests that not all altered melanocytes produce a visible nevus and may lose their ability to progress, explaining why precursor lesions cannot be identified for all melanomas. [11]

Direct exposure to ultraviolet (UV) light is the principal mechanism discussed in the literature as initiating the progression from precursor lesion to cancer. The threshold of UV exposure does not have to reach sunburn potential to cause damage as the skin's ability to repair damage varies from individual to individual.[12] It is thought that the latency period between exposure and melanoma development is approximately 20-40 years.[13]

There are two phases of growth for the melanoma lesion. The radius of the lesion can increase (radial growth phase) or the depth of the lesion can increase (vertical growth

phase). In 1969, Clark developed a classification system that describes the levels of microinvasion through the layers of the dermis and correlates with frequency of metastases and patient mortality.[3] In 1970, Breslow introduced a method to measure the depth of invasion in millimeters (tumor thickness) that correlates with patient survival.[14] Tumor thickness is considered the most important prognostic factor for melanoma.[15,16]

Melanoma can be categorized by histologic subtypes; the most common are superficial spreading, nodular, lentigo maligna, and acral lentiginous melanoma.[6,17,18] Superficial spreading melanoma is the most prevalent and has been found on any anatomic site. Acral lentiginous melanoma is a flat to nodular lesion with dark pigmentation that is found on the palms, soles and subungually. Nodular melanoma is an elevated lesion that is located on any anatomic site and is uniform in pigmentation. Lentigo maligna melanoma, also known as Hutchinson's freckle, is a macular lesion that is related to long-term sun exposure and is diagnosed most frequently on the face and ear.[19] However, nearly a third of tumors are of a histologic subtype not otherwise specified (NOS).[20]

INCIDENCE

The incidence of melanoma has been increasing dramatically since 1973 and continues to increase nearly three percent each year.[21] In 2012, the American Cancer Society estimates that 76,250 new cases will be diagnosed and melanoma is predicted to be the fifth leading site for cancer incidence for U.S. men (5%) and the sixth leading site for cancer incidence for U.S. women (4%).[22] The lifetime risk for developing melanoma is 1 in 36 for males and 1 in 55 for females based on data from 2006-2008.[22] This is an increase in the lifetime risk estimates from 2000-2001, which were 1 in 52 males and 1 in 77 females.[23] Between 1999 and 2008, both males and females had a significant increase in melanoma incidence – males had a 2.1 average annual percent change (AAPC) and females had an AAPC of 2.3.[22]

Melanoma is primarily diagnosed in whites; rates are 10 times higher in whites than in blacks. Hispanics in the United States have an increasing rate of melanoma and are diagnosed with late stage melanoma more often than non-Hispanic Whites.[24]

As age increases the incidence of melanoma increases; however, melanoma affects all age groups.[25] For males and females combined, individuals age 45 to 60 are diagnosed the most frequently. In a recent report, the American Cancer Society found that melanoma incidence increased for men over 55 years of age and for women of all

ages.[22] During the 1970s, the incidence rate of melanoma increased rapidly at approximately six percent per year and persons born prior to 1930 experienced the sharpest increases.[23,26] Younger cohorts that were born in the 1960's and 1970's in the U.S. and Australia have demonstrated a leveling off of incidence rates; this could be an effect of primary prevention public health programs.[27,28] **Incidence in the youngest age groups is rare and has not been well-described, thus is evaluated in greater detail in Chapter 1 of this dissertation.**

There has been a different rate of increase in the incidence of melanoma by body site.[27] For males, melanoma on the trunk has the highest incidence and has increased dramatically between 1973 and 2000; whereas for females, melanoma on the lower limbs has the highest incidence and has been increasing between 1973 and 2000.[6,28-32] Some research demonstrates that gender differences in tumor location may be due to differences in sun exposure behaviors, dressing, and clothing styles; however, other studies have not been able to support this finding. The theory that intermittent sun exposure (rather than chronic sun exposure) may lead to melanoma would explain why melanoma commonly arises on body sites that are infrequently exposed to the sun, i.e. on the trunk in males as opposed to the head.[11,33] Hemo et al. and Brady et al. found that tumors on more visible body areas are more likely to be diagnosed at an early stage.[34,35] While some studies have found a correlation between anatomic location and lesion thickness[35,36], other research has not been able to demonstrate these

associations.[34,37] Whiteman et al. hypothesize that an individual's predisposition to nevus development and sun exposure patterns drive the development of melanoma on different anatomic locations.[8,9] Infrequently, melanoma occurs on the palms and on the soles of the feet. Tumors found on these sites are distinctive because they often occur in any ethnicity, even without significant sun exposure.

Although the rate of melanoma incidence is increasing, these increases are seen largely in thin tumors consistent with superficial spreading melanoma. A recent report from the American Cancer Society found that only rates of localized disease increased (from 18.0 per 100,000 in 1999 to 22.2 per 100,000 in 2008), which is consistent with research that has shown that the incidence of thick melanomas has stabilized.[25,38-40] Other studies have shown that rates have increased for both thin and thick lesions.[41] The thickest lesions are seen in men and in older age groups and thin lesions are associated with younger patient age and higher educational level.[36,40]

While advancing technology and quality control methods have improved reporting [42], many central registries approximate that melanoma incidence is underestimated. It has been projected that as many as 20 percent of melanoma cases have not been reported, particularly in the earliest stages when many patients are diagnosed and treated in outpatient facilities instead of hospitals.[43,44] The possible underestimation of melanoma

incidence is an **important issue in New Jersey and is the basis for Chapter 2 of this dissertation.**

MORTALITY

Melanoma is responsible for about three-fourths of all deaths from skin cancer.[45] Approximately 4,910 U.S. men and 2,860 U.S. women were estimated to die from melanoma in 2005.[23] Age-adjusted mortality rates in the U.S. rose steadily until 1998, when the rate began decreasing in U.S. white men. Mortality rates in U.S. women began decreasing in 1988. However, overall mortality rates are not declining. Nearly one-fourth of melanoma patients are diagnosed before age 40; therefore, the years of life lost from melanoma are higher than for most other forms of cancer.[26] If analyzed by cohort, melanoma mortality rates level off, particularly in women in the young cohorts born after 1950.[46,47] In the 15-19 age group mortality trends are decreasing.

Although the cause-specific mortality rate (number of deaths from melanoma divided by the total population) is not decreasing over time, the case fatality rate (number of deaths from melanoma divided by the number of cases of melanoma during a specific time period) has steadily declined to less than 20%.[48] This paradox could be due to the fact that melanoma incidence is increasing even faster than the death rates are slowing (Figure 0-1).[44,49]

RISK FACTORS

The risk factors for melanoma can be endogenous (personal), exogenous (environmental), or a combination.

Endogenous/Personal/Constitutional Risk Factors

The most important independent, personal risk factor for melanoma is the density of melanocytic nevi (# of nevi per unit of skin surface).[4,5,25,27,29,50-53] Population-based and genetic studies have found a strong association between nevus development in children and the number of parental moles, which most likely points to an inherited factor.[4,54,55] In other studies, moderate sun exposure and sunburns induced melanocytic nevi during adolescence and early adulthood, thereby increasing the risk for melanoma.[4,54] Genetic predisposition to melanoma is also an important modifier of risk.[25,31,49,56-66] Twin studies, as well as studies of relatives of melanoma cases, consistently concluded that there is a strong inherited basis for the total number of melanocytic nevi and nevus density.[4,50,67]

When host susceptibility factors – fair skin, red hair, blue eyes, tendency to freckle, and propensity to burn – are combined they are deemed a sun-sensitive phenotype and independently increase an individual's risk for melanoma.[4,25,27,52,54,68-74] Brenner et al. used computer technology instead of self-report to reliably and objectively assess constitutive skin color and skin ultraviolet light sensitivity and observed an increased risk

of melanoma among subjects with the highest levels of sun exposure.[73] Luther et al. confirmed this observation in a population of children.[75] Immigrant studies reveal that a darker phenotype may be protective.[76]

The likelihood of developing melanoma increases as age increases. Several studies have found that different age cohorts have higher risks than others. Not only are older individuals more likely to have an increased risk of melanoma, they also have thicker lesions, are less likely to report itching or changes in the elevation of lesions, and are significantly more likely to report ulceration.[27,77] In a Swedish population-based study, individuals who were born before 1939 had a significant association between melanoma development and sunburns (OR=1.9, $p<0.05$) and between melanoma development and freckling (OR=2.0, $p<0.05$). Individuals who were born after 1939 had an increased risk of developing melanoma if there was a family history of melanoma (OR=2.2, $p<0.05$).[74]

Other endogenous risk factors that increase a person's risk of developing melanoma are: previous personal history of melanoma[27,52,78-80], history of melanoma in a first degree relative[27,52,58,74,81], geographical location[6], prior therapeutic irradiation from chemotherapy, or radiation treatment or other immunosuppression[52,82], xeroderma pigmentosum[12,27], and/or atypical mole syndrome or dysplastic nevus syndrome [25,52]. Obesity[69], pregnancy[83], estrogen/progesterone use[17,84,85], oral contraceptive use[86], and

hormonal and reproductive factors[87] have also been investigated but results have been inconsistent.

Exogenous/Environmental Risk Factors

Exposure to solar ultraviolet radiation (UV light) is well established as a major environmental risk factor for melanoma. However, the intensity, duration, and latitude of exposure are components of sun exposure which remain controversial.[50,88] Excessive intermittent sun exposure, similar to that received by indoor workers on weekends, holidays, or vacations, appears to be a higher risk than continual sun exposure that is received by outdoor workers.[4,19,25,27,54,74,89-95] It is possible that chronic exposure to the sun may have a protective effect (OR = 0.6 to 0.8) due to mechanisms in the skin.[90,93]

Sunburns, especially during childhood and adolescence, have been associated with melanoma development.[5,37,52,54,96,97] However, sunburns are not required for melanoma development because damage can be done when sun exposure is below the threshold of sunburns because individuals vary in their ability to repair sun damage.[4,12,98] The unreliability of sunburn history[99] may cause doubt in the relationship between sunburns and melanoma.

Poor sun protection behaviors, such as lack of sunscreen or not wearing protective clothing, exacerbate the effects of sun exposure.[30,51,91,92,100] Less than one-third of U.S. youth practiced routine sun protection on sunny days.[101] As children get older, the proportion using one or more sun-protective behaviors decreases. Studies conducted with high school populations reported a low use of sunscreens and the sunscreens that are used have an inadequate sun protection factor (SPF).[100,102] Individuals who are more likely to engage in sun-protective behaviors are older age, female gender, more sun sensitive, healthier, or know someone with skin cancer or melanoma.[92]

Some studies show that sunscreen use may be a risk factor for melanoma[13,96,103-109] because people who used sunscreens containing UVB-absorbing ingredients spend a longer time in the sun because they are not getting sunburns. However, the dose of UVA light is increased and melanocytic nevi may still develop.[4,25,51,88,95,106,110] Studies looking at the relationship between sunscreen use and the development of melanocytic nevi do not provide consistent results.[5,51,75,111,112] This may be could be because sunscreens could be preferentially used by individuals who are more at risk for melanoma; therefore, a protective behavior may appear as a risk factor if melanoma develops.[13,106,108] Also, it is possible that sunscreens are not being used properly, which may increase exposure to UV light.[13,111] For example, one study found that when youth reported that they used sunscreen, many did not reapply it when they stayed outside all day.[101] Finally, sunscreen use history may not be accurately reported.

Other exogenous risk factors that may increase an individual's risk of developing melanoma, but are not described in detail here, are: higher educational level[82,113], higher socioeconomic status[39,52,82], diet high in linoleic acid or alcohol[27,114], smoking[27], sunlamp use[47,52,54,68,96,115,116], and stress[27].

PREVENTION, SCREENING, AND EARLY DETECTION

Since melanoma etiology has not been clearly elucidated, primary prevention programs that could prevent the initiation of melanoma tumor cells primarily aim to reduce sunbathing, increase sunscreen use, and reduce tanning bed exposure.[25,47] Secondary prevention of melanoma is focused on identifying and treating people with established disease and those at very high risk of developing melanoma through early detection. There are several categories describing tools for the early detection of melanoma, including: digital photography, digital dermoscopy, confocal scanning laser microscopy, automated diagnosis systems, and screening.[25] Of these, screening for melanoma is the most beneficial because it is readily available and easy to perform.

Since screening is not beneficial for all types of cancer, it is important to describe that screening for melanoma could be beneficial for the following reasons[49,117]:

- Melanoma is a prevalent disease whose fatality can potentially be decreased.
- Most melanomas evolve through a relatively benign "preclinical" period, in which mortality after simple therapy (complete excision) is low or zero. Detection in the preclinical stages where it is easily treatable is essential to influence mortality due to cancer.
- Readily available, simple, noninvasive screening tests exist
- Treatment given after a positive test may be more effective than that which would be given later for clinically evident disease

While the American Academy of Dermatology[118], the American Cancer Society[22], and the National Institutes of Health (NIH) Consensus Conference[26] are in favor of routine screening for melanoma, the U.S. Preventive Services Task Force concluded that there was insufficient evidence for melanoma screening.[119] Regular examination of individuals at high risk by a primary care physician (PCPs) –selective screening- is also a controversial. In a study done by Weinstock et al., PCPs rarely recommended skin self-examinations or examined the body sites where melanomas frequently arise.[120] Marks found that physicians who were not trained were less likely to correctly diagnose melanoma.[121] Skin self-examination (SSE) has been found to be beneficial[25,122] as 6 to 50 percent of melanomas are self-detected.[123] **Chapter 3 of this dissertation will focus on the topic of SSE.**

SURVIVAL

The ten year relative survival rate after being diagnosed with melanoma is between 89 and 93%.[23,124] Over the past 60 years, the five-year survival rate for all stages of melanoma combined has increased from 40 percent in the 1940's to 91 percent in the 2000's.[23,85] If melanoma becomes metastatic the survival rate decreases dramatically. The five year survival rate is 6-15 percent and the median survival time is six to eight months.[22,125,126] Metastases to the liver, bone and/or brain have a median survival of three to four months.[126]

Tumor thickness is the major clinical prognostic factor for melanoma.[127-129] Other variables (not inclusive) that can be used to predict survival are age of the patient, ulceration, mitotic index, tumor infiltrating lymphocytes, and Clark level of invasion.[48,130-132] Females and younger age groups demonstrate better survival from melanoma, although the female survival rate declines in post-menopausal women.[133]

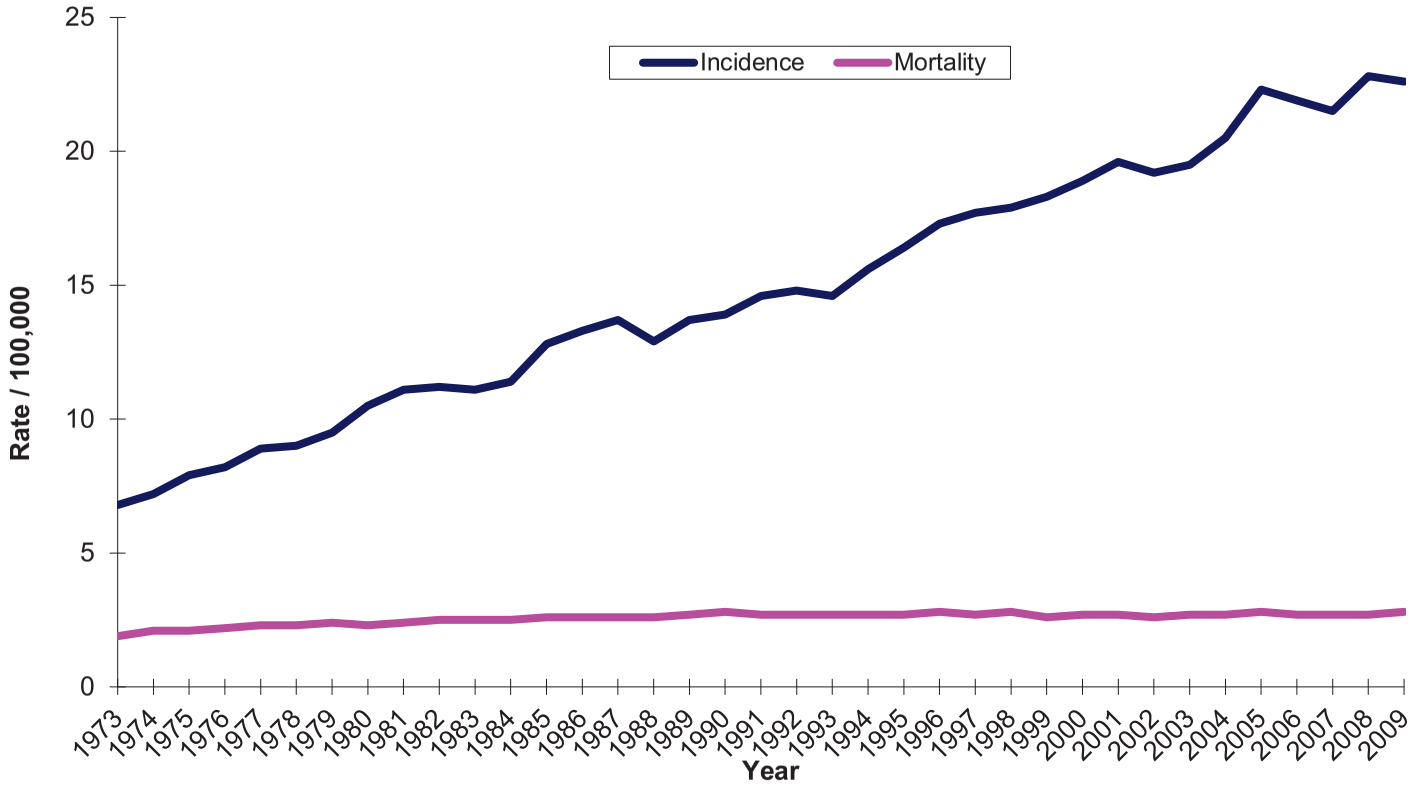
Different treatments may offer an extension of survival time. Unfortunately, the treatments that are available do not demonstrate prolonged survival time. Overall survival is approximately six to eight months with conventional chemotherapy and complete surgical resection has a median survival of 15 to 20 months with a 20 percent five-year survival rate.[125] Two newer targeted drugs, ipilimumab (Yervoy) and

vemurafenib (Zelboraf), have recently been approved by the FDA and may extend survival in people with advanced melanoma.[22]

SUMMARY

Melanoma is a major public health concern. The incidence of melanoma continues to rise and mortality rates are not declining in advanced stages of disease. This dissertation expounds on three salient issues in melanoma research. First, incidence rates in the youngest age groups are examined. Chapter 2 evaluates issues in melanoma surveillance. Finally, Chapter 3 addresses screening and survival.

FIGURE 0-1: MELANOMA INCIDENCE AND MORTALITY IN THE U.S., 1973-2009



Data are from SEER Program SEER*Stat database, NCI, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2012. Underlying mortality data provided by NCHS (www.cdc.gov/nchs). Incidence data are based on the SEER 9 Reg. Research data Nov 2011 submission. Rates are per 100,000 and age-adjusted to the 2000 US Std Population.

REFERENCES

(1) Green A, Trichopoulos D. Skin Cancer. In: Adami HO, Hunter D, Trichopoulos D, editors. Textbook of Cancer Epidemiology. Oxford: University Press, 2002: 281-300.

(2) Norris W. Case of fungoid disease. Edinburgh Med Surg Journal 1820; 16:562-565.

(3) Clark WHJ, Tucker MA. Problems with lesions related to the development of malignant melanoma: common nevi, dysplastic nevi, malignant melanoma in situ, and radial growth phase malignant melanoma. Human Pathology 1998; 29(1):8-14.

(4) Wiecker TS, Luther H, Buettner P, Bauer J, Garbe C. Moderate sun exposure and nevus counts in parents are associated with development of melanocytic nevi in childhood: a risk factor study in 1,812 kindergarten children. Cancer 2001; 97(3):628-638.

(5) Harrison SL, Buettner PG, MacLennan R. The North Queensland "Sun-Safe Clothing" study: design and baseline results of a randomized trial to determine the effectiveness of sun-protective clothing in preventing melanocytic nevi. American Journal of Epidemiology 2005; 161(6):536-545.

(6) Newell GR, Sider JG, Bergfelt L, Kripke ML. Incidence of cutaneous melanoma in the United States by histology with special reference to the face. Cancer Research 1988; 48(17):5036-5041.

(7) Morton DL, Essner R, Kirkwood JM, Wollman RC. The Skin - Malignant Melanoma. In: Kufe, Bast, Hait, Hong, Pollock, Weichselbaum et al., editors. Cancer Medicine. Hamilton: BC Decker, Inc., 2006: 1644-1662.

(8) Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. Journal of the National Cancer Institute 2003; 95(11):806-812.

(9) Carli P, Palli D. Re: Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. Journal of the National Cancer Institute 2003; 95(23):1801-1802.

(10) Armstrong BK. The Epidemiology of Melanoma: Where Do We Go From Here? In: Gallagher RP, Elwood JM, editors. Epidemiological Aspects of Cutaneous Malignant Melanoma. Norwell, MA: Kluwer Academic Publishers, 1994: 307-309.

(11) Harrison SL, Buettner PG, MacLennan R. Body-site distribution of melanocytic nevi in young Australian children. Archives of Dermatology 1999; 135(1):47-52.

(12) Berwick M, Vineis P. Markers of DNA repair and susceptibility to cancer in humans: an epidemiologic review. Journal of the National Cancer Institute 2000; 92(11):874-897.

(13) Berwick M, Fine JA, Barnhill RL. Can residual confounding explain the association between sunscreen use and skin cancer? American Journal of Epidemiology Supplement 1998; 147, S43. 1998.

(14) Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Annals of Surgery 1970; 172(5):902-908.

(15) Negin BP, Riedel E, Oliveria SA, Berwick M, Coit DG, Brady MS. Symptoms and signs of primary melanoma: important indicators of Breslow depth. Cancer 2003; 98(2):344-348.

(16) Friedman RJ, Rigel DS, Kopf AW. Early detection of malignant melanoma: the role of physician examination and self-examination of the skin. Ca: a Cancer Journal for Clinicians 1985; 35(3):130-151.

(17) Conti EM, Cercato MC, Gatta G, Ramazzotti V, Roscioni S, EUROCARE Working Group. Childhood melanoma in Europe since 1978: a population-based survival study. European Journal of Cancer 2001; 37(6):780-784.

(18) National Institutes of Health. NIH Consensus conference. Diagnosis and treatment of early melanoma. JAMA 1992; 268(10):1314-1319.

(19) Elwood JM, Gallagher RP. Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. International Journal of Cancer 1998; 78(3):276-280.

(20) Demierre MF, Chung C, Miller DR, Geller AC. Early detection of thick melanomas in the United States: beware of the nodular subtype. Archives of Dermatology 2005; 141(6):745-750.

(21) Dummer R, Bosch U, Panizzon R, Bloch PH , Burg G, Task F. Swiss guidelines for the treatment and follow-up of cutaneous melanoma . Dermatology 2001; 203(1):75-80.

(22) American Cancer Society. Cancer Facts & Figures 2012. Atlanta, GA: American Cancer Society, 2012.

(23) American Cancer Society. Cancer Facts & Figures 2006. Atlanta, GA: American Cancer Society, 2006.

(24) Cress RD, Holly EA. Incidence of cutaneous melanoma among non-Hispanic whites, Hispanics, Asians, and blacks: an analysis of California cancer registry data, 1988-93. Cancer Causes & Control 1997; 8(2):246-252.

(25) Oliveria S, Dusza S, Berwick M. Issues in the epidemiology of melanoma. Expert Review of Anticancer Therapy 2001; 1(3):453-459.

(26) Edman RL, Klaus SN. Is routine screening for melanoma a benign practice? JAMA 2000; 284(7):883-886.

(27) Marks R. Epidemiology of melanoma. Clinical & Experimental Dermatology 2000; 25(6):459-463.

(28) Hall HI, Miller DR, Rogers JD, Bewerse B. Update on the incidence and mortality from melanoma in the United States. Journal of the American Academy of Dermatology 1999; 40(1):35-42.

(29) Autier P, Boniol M, Severi G, Pedeux R, Grivegnee AR, Dore JF. Sex differences in numbers of nevi on body sites of young European children: implications for the etiology of cutaneous melanoma. Cancer Epidemiology, Biomarkers & Prevention 2004; 13(12):2003-2005.

(30) Chen YT, Dubrow R, Holford TR, Zheng T, Barnhill RL, Fine J et al. Malignant melanoma risk factors by anatomic site: a case-control study and polychotomous logistic regression analysis. International Journal of Cancer 1996; 67(5):636-643.

(31) Maldonado JL, Fridlyand J, Patel H, Jain AN, Busam K, Kageshita T et al. Determinants of BRAF mutations in primary melanomas. Journal of the National Cancer Institute 2003; 95(24):1878-1890.

(32) Robinson JK, Chmiel JS, Hartsell WF, Serwatka KN. Cutaneous Melanoma in Illinois: Change in Clinical Presentation over 20 Years. Cancer Incidence and End Results Committee.Chicago, IL: American Cancer Society,2003.

(33) Fears TR, Scotto J, Schneiderman MA. Mathematical models of age and ultraviolet effects on the incidence of skin cancer among whites in the United States. American Journal of Epidemiology 1977; 105(5):420-427.

(34) Brady MS, Oliveria SA, Christos PJ, Berwick M, Coit DG, Katz J et al. Patterns of detection in patients with cutaneous melanoma. Cancer 2000; 89(2):342-347.

(35) Hemo Y, Gutman M, Klausner JM. Anatomic site of primary melanoma is associated with depth of invasion. Archives of Surgery 1999; 134(2):148-150.

(36) Sander B, Karlsson P, Rosdahl I, Westermark P, Boeryd B. Cutaneous malignant melanoma in Swedish children and teenagers 1973-1992: a clinico-pathological study of 130 cases. International Journal of Cancer 1999; 80(5):646-651.

(37) Weinstock MA, Colditz GA, Willett WC, Stampfer MJ, Bronstein BR, Mihm MC, Jr. et al. Melanoma and the sun: the effect of swimsuits and a "healthy" tan on the risk of nonfamilial malignant melanoma in women . American Journal of Epidemiology 1991; 134(5):462-470.

(38) Lipsker DM, Hedelin G, Heid E, Grosshans EM, Cribier BJ. Striking increase of thin melanomas contrasts with stable incidence of thick melanomas. Archives of Dermatology 1999; 135(12):1451-1456.

(39) Berwick M. Why are people still dying from melanoma? Archives of Dermatology 1999; 135(12):1534-1536.

(40) Garbe C, McLeod GR, Buettner PG. Time trends of cutaneous melanoma in Queensland, Australia and Central Europe. Cancer 2000; 89(6):1269-1278.

(41) Purdue MP, Freeman LE, Anderson WF, Tucker MA. Recent trends in incidence of cutaneous melanoma among US Caucasian young adults. Journal of Investigative Dermatology 2008; 128(12):2905-2908.

(42) Richard MA. Screening and diagnosis: What is the result of the audit? How to explain the increasing melanoma incidence and the stable mortality? Melanoma Research 2003; 13(4): A23.

(43) Jemal A, Devesa SS, Hartge P, Tucker MA . Recent trends in cutaneous melanoma incidence among whites in the United States. Journal of the National Cancer Institute 2002; 93(9):678-683.

(44) Lamberg L. "Epidemic" of malignant melanoma. JAMA 2002; 287(17), 2201.

(45) National Cancer Institute. Screening for Skin Cancer (PDQ). Bethesda, MD: National Cancer Institute, 1998.

(46) Marks R. Two decades of the public health approach to skin cancer control in Australia: why, how and where are we now? Australasian Journal of Dermatology 1999; 40(1):1-5.

(47) Weinstock MA. Issues in the epidemiology of melanoma. Hematology - Oncology Clinics of North America 1998; 12(4):681-698.

(48) Schuchter L, Schultz DJ, Synnestvedt M, Trock BJ, Guerry D, Elder DE et al. A prognostic model for predicting 10-year survival in patients with primary

melanoma. The Pigmented Lesion Group. Annals of Internal Medicine 1996; 125(5):369-375.

(49) Masri GD, Clark WHJ, Guerry D, Halpern A, Thompson CJ, Elder DE. Screening and surveillance of patients at high risk for malignant melanoma result in detection of earlier disease. Journal of the American Academy of Dermatology 1990; 22 (6 Pt 1):1042-1048.

(50) Autier P, Severi G, Pedeux R, Cattaruzza MS, Boniol M, Grivegnee A et al. Number and size of nevi are influenced by different sun exposure components: implications for the etiology of cutaneous melanoma (Belgium, Germany, France, Italy). Cancer Causes & Control 2003; 14(5):453-459.

(51) Autier P, Dore JF, Cattaruzza MS, Renard F, Luther H, Gentiloni-Silverj F et al. Sunscreen use, wearing clothes, and number of nevi in 6- to 7-year-old European children. European Organization for Research and Treatment of Cancer Melanoma Cooperative Group.[comment]. Journal of the National Cancer Institute 1998; 90(24):1873-1880.

(52) Rigel DS, Carucci JA. Malignant melanoma: prevention, early detection, and treatment in the 21st century. Ca: a Cancer Journal for Clinicians 2000; 50(4):215-36.

(53) Rodenas JM, Delgado-Rodriguez M, Farinas-Alvarez C, Herranz MT, Serrano S. Melanocytic nevi and risk of cutaneous malignant melanoma in southern Spain. American Journal of Epidemiology 1997; 145(11):1020-1029.

(54) Veierod MB, Weiderpass E, Thorn M, Hansson J, Lund E, Armstrong B et al. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. Journal of the National Cancer Institute 2003; 95(20):1530-1538.

(55) Tucker MA, Goldstein AM. Melanoma etiology: where are we? Oncogene 2003; 22(20):3042-3052.

(56) Berwick M. Gene-environment interaction in melanoma. Forum 2000; 10(3):191-200.

(57) Goldstein AM, Falk RT, Fraser MC, Dracopoli NC, Sikorski RS, Clark WH, Jr. et al. Sun-related risk factors in melanoma-prone families with CDKN2A mutations. Journal of the National Cancer Institute 1998; 90(9):709-711.

(58) Greene MH. The genetics of hereditary melanoma and nevi. 1998 update. Cancer 1999; 86(11 Suppl):2464-2477.

(59) Goggins WB, Tsao H. A population-based analysis of risk factors for a second primary cutaneous melanoma among melanoma survivors. Cancer 2001; 97(3):639-643.

(60) Dwyer T, Stankovich JM, Blizzard L, FitzGerald LM, Dickinson JL, Reilly A et al. Does the addition of information on genotype improve prediction of the risk of melanoma and nonmelanoma skin cancer beyond that obtained from skin phenotype? American Journal of Epidemiology 2001; 159(9):826-833.

(61) MacKie RM, Andrew N, Lanyon WG, Connor JM. CDKN2A germline mutations in U.K. patients with familial melanoma and multiple primary melanomas. Journal of Investigative Dermatology 1998; 111(2):269-272.

(62) Bressac-de Paillerets B, Avril MF. How much genetics of melanoma can be transferred in patient counseling? Melanoma Research 2003; 13(4): A16-A17.

(63) Goldstein AM, Martinez M, Tucker MA, Demenais F. Gene-covariate interaction between dysplastic nevi and the CDKN2A gene in American melanoma-prone families. Cancer Epidemiology, Biomarkers & Prevention 2000; 9(9):889-894.

(64) Chaudru V, Chompret A, Bressac-de P, Spatz A, Avril MF, Demenais F. Influence of genes, nevi, and sun sensitivity on melanoma risk in a family sample unselected by family history and in melanoma-prone families. Journal of the National Cancer Institute 2004; 96(10):785-795.

(65) Geradts J, Wilentz R, Roberts H. utImmunohistochemical Detection of the Alternate INK4a-encoded Tumor Suppressor Protein p14(ARF) in Archival Human Cancers and Cell Lines Using Commercial Antibodies: Correlation with p16(INK4a) Expression. Modern Pathology 2001; 14(11), 1162-1168.

(66) Hogg D, Brill H, Liu L, Monzon J, Summers A, From L et al. Role of the cyclin-dependent kinase inhibitor CDKN2A in familial melanoma. Journal of Cutaneous Medicine & Surgery 1998; 2(3):172-179.

(67) Bataille V, Snieder H, MacGregor AJ, Sasieni P, Spector TD. Genetics of risk factors for melanoma: an adult twin study of nevi and freckles. Journal of the National Cancer Institute 2000; 92(6):457-463.

(68) Boniol M, Autier P, Dore JF. Re: A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. Journal of the National Cancer Institute 2004; 96(4):335.

(69) Holly EA, Aston DA, Cress RD, Ahn DK, Kristiansen JJ. Cutaneous melanoma in women. II. Phenotypic characteristics and other host-related factors. American Journal of Epidemiology 1995; 141(10):934-942.

(70) Naldi L, Lorenzo I, Parazzini F, Gallus S, La V. Pigmentary traits, modalities of sun reaction, history of sunburns, and melanocytic nevi as risk factors for cutaneous malignant melanoma in the Italian population: results of a collaborative case-control study. Cancer 2000; 88(12):2703-2710.

(71) Cress RD, Holly EA, Ahn DK. Cutaneous melanoma in women. V. Characteristics of those who tan and those who burn when exposed to summer sun. Epidemiology 1995; 6(5):538-543.

(72) Barker D, Dixon K, Medrano EE, Smalara D, Im S, Mitchell D et al. Comparison of the responses of human melanocytes with different melanin contents to ultraviolet B irradiation. Cancer Research 1995; 55(18):4041-4046.

(73) Brenner AV, Lubin JH, Calista D, Landi MT. Instrumental measurements of skin color and skin ultraviolet light sensitivity and risk of cutaneous malignant melanoma: a case-control study in an Italian population. American Journal of Epidemiology 2002; 156(4):353-362.

(74) Masback A, Westerdahl J, Ingvar C, Olsson H, Jonsson N. Clinical and histopathological characteristics in relation to aetiological risk factors in cutaneous melanoma: a population-based study. Melanoma Research 1999; 9(2):189-197.

(75) Luther H, Altmeyer P, Garbe C, Ellwanger U, Jahn S, Hoffmann K et al. Increase of melanocytic nevus counts in children during 5 years of follow-up and analysis of associated factors. Archives of Dermatology 1996; 132(12):1473-1478.

(76) Khlat M, Vail A, Parkin M, Green A. Mortality from melanoma in migrants to Australia: variation by age at arrival and duration of stay. American Journal of Epidemiology 1992; 135(10):1103-1113.

(77) Christos PJ, Oliveria SA, Berwick M, Guerry D, Elder DE, Synnestvedt M et al. Signs and symptoms of melanoma in older populations. Journal of Clinical Epidemiology 2000; 53(10):1044-1053.

(78) Giles G, Staples M, McCredie M, Coates M. Multiple primary melanomas: an analysis of cancer registry data from Victoria and New South Wales. Melanoma Research 1995; 5(6):433-438.

(79) Bhatia S, Estrada-Batres L, Maryon T, Bogue M, Chu D. Second primary tumors in patients with cutaneous malignant melanoma. Cancer 1999; 86(10):2014-2020.

(80) DiFronzo LA, Wanek LA, Elashoff R, Morton DL. Increased incidence of second primary melanoma in patients with a previous cutaneous melanoma. Annals of Surgical Oncology 1999; 6(7):705-711.

(81) Aitken JF, Duffy DL, Green A, Youl P, MacLennan R, Martin NG. Heterogeneity of melanoma risk in families of melanoma patients . American Journal of Epidemiology 1994; 140(11):961-973.

(82) Goggins WB, Finkelstein DM, Tsao H. Evidence for an association between cutaneous melanoma and non-Hodgkin lymphoma. Cancer 2001; 91(4):874-880.

(83) Daryanani D, Plukker JT, De H, Kuiper H , Nap RE, Hoekstra HJ. Pregnancy and early-stage melanoma. Cancer 2001; 97(9):2248-2253.

(84) Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women: ovulatory life, menopause, and use of exogenous estrogens. Cancer Epidemiology, Biomarkers & Prevention 1994; 3(8):661-668.

(85) Friedman RJ, Rigel DS, Silverman MK, Kopf AW, Vossaert KA. Malignant melanoma in the 1990s: the continued importance of early detection and the role of physician examination and self-examination of the skin. Ca: a Cancer Journal for Clinicians 1991; 41(4):201-226.

(86) Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women. III. Reproductive factors and oral contraceptive use. American Journal of Epidemiology 1995; 141(10):943-950.

(87) Smith MA, Fine JA, Barnhill RL, Berwick M. Hormonal and reproductive influences and risk of melanoma in women. International Journal of Epidemiology 1998; 27(5):751-757.

(88) Wang SQ, Setlow R, Berwick M, Polsky D, Marghoob AA, Kopf AW et al. Ultraviolet A and melanoma: a review. Journal of the American Academy of Dermatology 2001; 44(5):837-846.

(89) Elwood JM. Melanoma and sun exposure. Seminars in Oncology 1996; 23(6):650-666.

(90) Walter SD, King WD, Marrett LD. Association of cutaneous malignant melanoma with intermittent exposure to ultraviolet radiation: results of a case-control study in Ontario, Canada. International Journal of Epidemiology 1999; 28(3):418-427.

(91) Campbell HS, Birdsell JM. Knowledge, beliefs, and sun protection behaviors of Alberta adults. Preventive Medicine 1994; 23(2):160-166.

(92) Weinstock MA, Rossi JS, Redding CA, Maddock JE, Cottrill SD. Sun protection behaviors and stages of change for the primary prevention of skin cancers among beachgoers in southeastern New England. Annals of Behavioral Medicine 2000; 22(4):286-293.

(93) Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. International Journal of Cancer 1997; 73(2):198-203.

(94) Holman CD, Mulroney CD, Armstrong BK. Epidemiology of pre-invasive and invasive malignant melanoma in Western Australia . International Journal of Cancer 1980; 25(3):317-323.

(95) Gasparro FP, Berwick M. Re: Sunscreen use, wearing clothes, and number of nevi in 6- to 7-year-old European children. Journal of the National Cancer Institute 1999; 91(12):1078-1080.

(96) Holly EA, Aston DA, Cress RD, Ahn DK, Kristiansen JJ. Cutaneous melanoma in women. I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. American Journal of Epidemiology 1995; 141(10):923-933.

(97) Weinstock MA, Colditz GA, Willett WC, Stampfer MJ, Bronstein BR, Mihm MCJ et al. Nonfamilial cutaneous melanoma incidence in women associated with sun exposure before 20 years of age. Pediatrics 1989; 84(2):199-204.

(98) Johnson DS, Yamane S, Morita S, Yonehara C, Wong JH. Malignant melanoma in non-Caucasians: experience from Hawaii. Surgical Clinics of North America 2003; 83(2):275-282.

(99) Berwick M, Chen YT. Reliability of reported sunburn history in a case-control study of cutaneous malignant melanoma. American Journal of Epidemiology 1995; 1995 Jun 1;141(11):1033-1037.

(100) Hall HI, May DS, Lew RA, Koh HK, Nadel M. Sun protection behaviors of the U.S. white population. Preventive Medicine 1997; 26(4):401-407.

(101) Cokkinides VE, Johnston-Davis K, Weinstock M, O'Connell MC, Kalsbeek W, Thun MJ et al. Sun exposure and sun-protection behaviors and attitudes among U.S. youth, 11 to 18 years of age. Preventive Medicine 2001; 33(3):141-151.

(102) Centers for Disease Control and Prevention. Sun-protection behaviors used by adults for their children--United States, 1997. JAMA 1998; 280(4):317-318.

(103) Drolet BA, Connor MJ. Sunscreens and the prevention of ultraviolet radiation-induced skin cancer. Journal of Dermatologic Surgery & Oncology 1992; 18(7):571-576.

(104) Huncharek M, Kupelnick B. Use of topical sunscreens and the risk of malignant melanoma: a meta-analysis of 9067 patients from 11 case-control studies. American Journal of Public Health 2002; 92(7):1173-1177.

(105) Chiang TM, Sayre RM, Dowdy JC, Wilkin NK, Rosenberg EW. Sunscreen ingredients inhibit inducible nitric oxide synthase (iNOS): a possible biochemical explanation for the sunscreen melanoma controversy. Melanoma Research 2005; 15:3-6.

(106) Autier P, Dore JF, Renard F, Luther H, Cattaruzza MS, Gefeller O et al. Melanoma and sunscreen use: need for studies representative of actual behaviours. Melanoma Research 1997; 7(Suppl 2):S115-S120.

(107) Autier P, Dore JF, Schifflers E, Cesarini JP, Bollaerts A, Koelmel KF et al. Melanoma and use of sunscreens: an Eortc case-control study in Germany, Belgium and France. The EORTC Melanoma Cooperative Group. International Journal of Cancer 1995; 61(6):749-755.

(108) Westerdahl J, Olsson H, Masback A, Ingvar C, Jonsson N. Is the use of sunscreens a risk factor for malignant melanoma? Melanoma Research 1995; 5(1):59-65.

(109) Elwood JM, Gallagher RP. More about: sunscreen use, wearing clothes, and number of nevi in 6- to 7-year-old European children. Journal of the National Cancer Institute 1999; 91(13):1164-1166.

(110) Diffey BL, Healy E, Thody AJ, Rees JL. Melanin, melanocytes, and melanoma. Lancet 1995; 346(8991-8992):1713.

(111) Autier P, Dore JF, Negrier S, Lienard D, Panizzon R, Lejeune FJ et al. Sunscreen use and duration of sun exposure: a double-blind, randomized trial. Journal of the National Cancer Institute 1999; 91(15):1304-1309.

(112) 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):2955-2960.

(113) White E, Kirkpatrick CS, Lee JA. Case-control study of malignant melanoma in Washington State. I. Constitutional factors and sun exposure. American Journal of Epidemiology 1994; 139(9):857-868.

(114) Millen AE, Tucker MA, Hartge P, Halpern A, Elder DE, Guerry D et al. Diet and melanoma in a case-control study. Cancer Epidemiology, Biomarkers & Prevention 2004; 13(6):1042-1051.

(115) Chen YT, Dubrow R, Zheng T, Barnhill RL, Fine J, Berwick M. Sunlamp use and the risk of cutaneous malignant melanoma: a population-based case-control study in Connecticut, USA. International Journal of Epidemiology 1998; 27(5):758-765.

(116) Cokkinides VE, Weinstock MA, O'Connell MC, Thun MJ. Use of indoor tanning sunlamps by US youth, ages 11-18 years, and by their parent or guardian caregivers: prevalence and correlates. Pediatrics 2002; 109(6):1124-1130.

(117) Weiss NS. Outcome events in studies of diagnostic or screening tests. Journal of Medical Screening 2002; 9(2):52-53.

(118) Robinson JK, Rigel DS, Amonette RA. What promotes skin self-examination? Journal of the American Academy of Dermatology 1998; 38(5 Pt 1):752-757.

(119) Wolff T, Tai E, Miller T. Screening for skin cancer: an update of the evidence for the U.S. Preventive Services Task Force. Annals of Internal Medicine 2009; 150(3):194-198.

(120) Weinstock MA, Martin RA, Risica PM, Berwick M, Lasater T, Rakowski W et al. Thorough skin examination for the early detection of melanoma. American Journal of Preventive Medicine 1999; 17(3):169-175.

(121) Marks R. Prevention and control of melanoma: the public health approach. Ca: a Cancer Journal for Clinicians 1996; 46(4):199-216.

(122) Berwick M, Begg CB, Fine JA, Roush GC, Barnhill RL. Screening for cutaneous melanoma by skin self-examination. Journal of the National Cancer Institute 1996; 88(1):17-23.

(123) Friedman LC, Bruce S, Webb JA, Weinberg AD, Cooper HP. Skin self-examination in a population at increased risk for skin cancer. American Journal of Preventive Medicine 1993; 9(6):359-364.

(124) McKinnon JG, Yu XQ, McCarthy WH, Thompson JF. Prognosis for patients with thin cutaneous melanoma: long-term survival data from New South Wales Central Cancer Registry and the Sydney Melanoma Unit. Cancer 2003; 98(6):1223-1231.

(125) Hsueh EC, Essner R, Foshag LJ, Ollila DW, Gammon G, O'Day SJ et al. Prolonged survival after complete resection of disseminated melanoma and active immunotherapy with a therapeutic cancer vaccine. Journal of Clinical Oncology 2001; 20(23):4549-4554.

(126) Sun W, Schuchter LM. Metastatic melanoma. Current Treatment Options in Oncology 2001; 2001 Jun;2(3):193-202.

(127) Schwartz JL, Mozurkewich EL, Johnson TM. Current management of patients with melanoma who are pregnant, want to get pregnant, or do not want to get pregnant. Cancer 2001; 97(9):2130-2133.

(128) DiFronzo LA, Wanek LA, Morton DL. Earlier diagnosis of second primary melanoma confirms the benefits of patient education and routine postoperative follow-up. Cancer 2001; 91(8):1520-1524.

(129) Berwick M. Evaluating early detection in the diagnosis of melanoma. Archives of Dermatology 2006; 142(11):1485-1486.

(130) Barnhill RL, Fine JA, Roush GC, Berwick M. Predicting five-year outcome for patients with cutaneous melanoma in a population-based study.[erratum appears in Cancer 1997 Jan 15;79(2):423]. Cancer 1996; 78(3):427-432.

(131) Gamel JW, George SL, Edwards MJ, Seigler HF. The long-term clinical course of patients with cutaneous melanoma. Cancer 2002; 95(6):1286-1293.

(132) Masback A, Olsson H, Westerdahl J, Ingvar C, Jonsson N. Prognostic factors in invasive cutaneous malignant melanoma: a population-based study and review. Melanoma Research 2001; 11(5):435-445.

(133) Blois MS, Sagebiel RW, Abarbanel RM, Caldwell TM, Tuttle MS. Malignant melanoma of the skin. I. The association of tumor depth and type, and patient sex, age, and site with survival. Cancer 1983; 52(7):1330-1341.

CHAPTER 1 MELANOMA INCIDENCE IN CHILDREN AND ADOLESCENTS IN THE UNITED STATES, 1995-2008

ABSTRACT

BACKGROUND: The increasing incidence of melanoma is not limited to the adult population; since 1975 the childhood melanoma rates have risen every year, accounting for 1 to 3 percent of melanoma cases. Because of the rarity of melanoma in children and the difficulty in differentiating tumor types, 40 to 60 percent of childhood melanoma cases are initially misdiagnosed. The purpose of this study was to examine differences between children/adolescents and adults in demographic and clinical characteristics of melanoma. METHODS: Melanoma cases were identified using the CINA Deluxe database that is compiled by the North American Association of Central Cancer Registries (NAACCR) and includes diagnoses between the years 1995-2008. Melanoma frequency distributions and average annual incidence rates by age, gender, stage, histologic subtype, anatomic site, diagnostic confirmation, Breslow depth, race, and ethnicity were generated. Chi square (x^2) statistics and were calculated to investigate differences in categorical variables. Rate ratios are presented. Confidence intervals for the age-adjusted rate ratios were calculated using the Tiwari method. Annual percent change (APC) was calculated using weighted least squares methods and significance was set as p-value less than 0.05. RESULTS: From 1995 to 2008, there were 4,845 melanomas reported to central cancer registries in individuals who were younger than age 20. In the youngest age group of children less than one year of age there were

110 (2.3%) reported cases of melanoma, 138 (2.8%) were in the 1-4 age group, 278 (5.7%) were in the 5-9 age group, 793 (16.4%) were in the 10-14 age group, and 3,526 (72.8%) were in the 15-19 year old age group. Individuals in the youngest age group (ages 0-9) had statistically significantly more melanomas diagnosed in the late stages than did the two older age groups (x^2 = 63.59; p<.0001). Additionally, the youngest and oldest age groups had significantly more melanoma with a Breslow depth greater than 4.00 mm – 19.9 % and 21.3 %, respectively (x^2 = 22.3; p<0.0001) compared to the middle-aged. Gender differences start at age 10 when female incidence begins to surpass that of males until ages 45-49 when there is an upturn in male incidence rates. Rates were statistically different by gender ($p < 0.05$) for every age group beginning at age 15. CONCLUSION: Melanoma incidence in children is significantly different than adults by stage, Breslow depth, race, ethnicity, and gender. This study adds valuable epidemiologic information for the youngest age groups; however, more research is necessary to learn why these differences are occurring.

BACKGROUND

Although melanoma represents one of the most rapidly increasing cancers in adults[1], and the rising incidence in adolescents has been documented world-wide[2], melanoma is not commonly studied in the youngest children (0-9 years).

Melanoma is rare in children and adolescents, accounting for 1 to 3 percent of the melanoma cases in the U.S.[3,4] Children under the age of 10 account for 0.3 to 0.4 percent of melanoma cases.[5] Because of the rarity of melanoma in children and the difficulty in differentiating tumor types, 40 to 60 percent of childhood melanoma cases are misdiagnosed.[4,6-9] Initial misdiagnosis may lead to a delay in treatment (40 percent of cases) or improper treatment, causing nearly one half of the deaths from childhood melanoma.[4] The five-year survival rate for children diagnosed with melanoma is only 77 percent[10,11] compared to 91 percent in the adult population.[1] The time to recurrent disease is shorter (6.2 years) than in adults (8.4 years) and if the melanoma returns the five-year survival rate further decreases to 33 percent.[5] Delays in treatment due to misdiagnosis negatively affect survival rates.

Much of the literature regarding childhood melanoma are case reports or small single-institution reports and provide inconsistent results about the similarities of melanoma in children and adults. Of the few population-based studies that have been published

(Table 1-1), there is conflicting evidence that melanoma in childhood is no different in terms of biological behavior from adult melanoma. In a population-based study using the Australian Paediatric Cancer Registry, there were 217 melanoma cases in children under 15 years of age identified over a 17-year period, with the most common site being the trunk and a male/female ratio of 0.92.[12] Using slightly more recent years of the same dataset, there was no difference in the site distribution of males and females among children.[13] Whiteman et al. conducted the first case-control study of melanoma among children under the age of 15 years in Queensland, Australia and found that the melanoma risk increased with multiple large nevi and sun sensitive phenotypic characteristics – analogous to studies of melanoma in adults.[14] There have been three published population-based studies of childhood melanoma in the U.S. Strouse et al. analyzed children and young adults with melanoma included in the Surveillance, Epidemiology, and End Results (SEER) database from 1973-2001 and found that melanoma is increasing rapidly in children, particularly in adolescents. Patients who were younger than 20 had a similar prognosis to adults; although the association could not be fully assessed due to the limited number of cases. They also note that, compared with adolescents and young adults, young children (<10 years) with melanoma are more likely to have metastasis, thick primaries, and high risk biology.[15] Hamre et al. found that females represented a higher proportion of childhood/adolescent cases of melanoma in individuals younger than age 20 in the 1973-1996 SEER data.[16] Finally, Wu et al. used a larger, more representative, U.S. population-based dataset from the National Association of Central Cancer Registries (NAACCR) to analyze all types of cancer

in 15-49 year olds, which included melanoma.[17] This study also found a preponderance of melanoma in young women; however, the youngest age categories were not included in the analysis.

The purpose of this study was to examine the incidence of melanoma diagnosed in children 0-19 using U.S., population-based data from the North American Association of Central Cancer Registries (NAACCR) and to compare these patterns with those seen in adults by personal and clinical characteristics. This dataset provided incidence data from the largest population-based study of childhood melanoma in the U.S. and provided data on the youngest age groups that can be used as a baseline for future research.

METHODS

DATA

Melanoma cases were identified using the CINA Deluxe database that is compiled by the North American Association of Central Cancer Registries (NAACCR) and includes diagnoses between the years 1995-2008. These data are based on the NAACCR December 2011 data submission. The CINA Deluxe database includes population-based central cancer registries in the United States that met the NAACCR high quality criteria for incidence data, which includes: (1) a completeness estimate of 90 percent or better

for each year in the dataset; (2) five percent or fewer are reported from death certificates as the only source per year; (3) 100 percent of the cases passed EDITS (NAACCR quality control); (4) 2 of 1000 or fewer duplicate records for 1995-2008 combined; (5) 3 percent or fewer cases with missing information in the sex, age, or county fields; (6) 5 percent or fewer with missing information in the race field; and, (7) data were submitted within 23 months of the close of the diagnosis year. Fifty-three member registries consented to participate in this study. Melanoma data from Washington DC and forty-seven states (Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, Washington, West Virginia, Wisconsin, and Wyoming) were included. Five metropolitan area registries (Los Angeles, Greater Bay, Atlanta, Detroit, and Seattle) were excluded to avoid duplication with state data. Analyses involving time trends include only data from registries that have data for all years in the time interval under investigation to avoid inaccurate conclusions based on skewed data.

Cancer cases included in this study were coded according to the *International Classification of Diseases for Oncology*, *Third Edition* (ICD-O-3) for primary site (C440-

C449) and histology (8720-8790) for melanoma of the skin. All cases considered for analysis had invasive behavior. Invasive melanoma of the skin / cutaneous melanoma is hereafter referred to as 'melanoma' in this paper. The variables from the CINA Deluxe database that were required for this analysis included: year of diagnosis, age, race/ethnicity, gender, registry, primary site, morphology, topography, histologic confirmation, behavior, grade, sequence number, summary stage and type of reporting source.

Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 7.1.0 was used for analysis. SEER*Stat uses population estimates from the US Census Bureau's Population Estimates Program, in collaboration with the National Center for Health Statistics (http://seer.cancer.gov/popdata/methods.html).[18] Age-specific rates were calculated for each 5-year age group. Rates for intervals of age exceeding 5 years are age-adjusted to the 2000 U.S. standard population. In order to maintain reliable estimates, incidence rates and counts were suppressed where counts were fewer than 6, as required by NAACCR. Therefore, absence of a data point means that the figure was not evaluable and not that the rate was zero, unless otherwise indicated. Denominators were calculated as person-years. State populations were only used in rate calculations if case counts were available for that year and only states with complete years of data for the study period were included. Generally, most analyses were conducted for the years

2003-2008 to provide the most stable rates. Counts of melanoma were based on data from 1995-2008; however, some states did not submit data for each year causing an underestimate of cases. For time trends, data from 1999-2008 were used; thus data from Arkansas, Mississippi, New York, North Carolina, South Dakota, Tennessee, Virginia, Washington DC, and Wyoming were excluded because data were not available all years in these states.

Melanoma frequency distributions and average annual incidence rates by age, gender, stage, histologic subtype, anatomic site, diagnostic confirmation, Breslow depth, race, and ethnicity were generated. Chi square (x^2) statistics were used to investigate whether distributions of categorical variables differed from one another. Rate ratios with 95 percent confidence intervals (95 % CI) for the age-adjusted rate ratios were calculated using the method from Tiwari et al.[19] Annual percent change (APC) was calculated using weighted least squares methods and significance was set as *p*-value less than 0.05.

Where possible, age was broken down by the four youngest age groups (0, 1-4, 5-9, 10-14). Otherwise, age categories were collapsed into 10-year age groups for comparison purposes. Children were considered to be ages 0-9 and adolescents were considered to be in the 10-19 age group. Summary stage was grouped into localized, regional, distant metastases, and unknown / unstaged categories. Diagnosis years 2001-2003 were

staged according to SEER summary stage 2000 and diagnosis years 2004-2008 were staged according to the derived SEER summary stage 2000 (SS2000).[20] For the youngest age groups where counts were not adequate by stage, localized stage was considered 'early stage' and regional and distant metastases stages were condensed into a 'late stage' category. Anatomic site categories were: Skin of trunk (C44.5), skin of upper limb and shoulder (C44.6), skin of lower limb and hip (C44.7), head & neck (C44.0-skin of lip, C44.1-eyelid, C44.2-External ear, C44.3-Skin other/unspecified parts of face, C44.4-skin of scalp and neck), and skin, not otherwise specified NOS (C44.9). Extremely small numbers (< 0.10 %) caused the exclusion of C44.8-Overlapping lesion of skin.

Ninety-eight percent of tumors in children and adolescents (2562 / 2608) and in adults (308,112 / 314,041) were coded as unknown grade. Therefore, this variable was not included in the analysis.

Race and ethnicity were categorized by NAACCR Hispanic Identification Algorithm (NHIA), which combines direct and indirect methods of identifying individuals of Hispanic ethnicity. Often direct methods (identification of ethnicity in a medical record) are limited; however the race/ethnicity can be determined using death certificates, surname and maiden name matching algorithms, birth place, information from special studies, physician follow-up, or linkages with other data sources (indirect methods).[21]

RESULTS

From 1995 to 2008, there were 4,845 melanomas reported to central cancer registries in individuals who were younger than age 20. Of these, only 110 (2.3%) occurred in children less than one year of age, 138 (2.8%) in the 1-4 age group, 278 (5.7%) in the 5-9 age group, 793 (16.4%) in the 10-14 age group, and 3,526 (72.8%) in the 15-19 year old age group. Of the individuals diagnosed with melanoma in the 0-19 age group, 99 percent had histologic confirmation, which was similar to adults (98.9 %).

Anatomic Site

Figure 1-1 shows the distribution of melanoma diagnosed by anatomic site. Melanomas diagnosed in males in the 0-9 age group were primarily found in the 'Head & Neck' (30.9 %) and secondarily in the 'Upper Limb & Shoulder' (23.8%). Melanomas diagnosed in females in the 0-9 age group were primarily in the 'Lower limb & Hip' (29.5%), which was closely followed by tumors of the 'Head & Neck' (27.2 %). Patterns change in the 10-19 age group for males and melanoma of the 'Trunk' was predominant (40.9%) and 'Head & Neck' was the second highest proportion (28.0%), which is consistent with what is seen in adult men. Unlike males, patterns seen in females ages 10-19 were not similar to that seen in adult women. The highest proportion of melanomas in the 10-19 year old age group were diagnosed in the 'Trunk' (38.4%) followed by 'Lower limb & Hip' (26.5%), whereas in adult women the highest proportion are diagnosed in both the upper and lower limbs. Chi square tests for the association between gender and

anatomic site was not significant for the 0-9 age group (x^2=6.31, p=0.17), but there was significant relationship for individuals age 10-19 (x^2=221.68, p=0<0.0001).

Of note is the increase in the proportion of melanomas diagnosed on the trunk of males and female in the 10-19 age group, where the percentage of cases found on the trunk doubles for males and nearly doubles for females, although not statistically significant (x^2 = 2.86, p = 0.09). Incidence rates by anatomic site for the 0-19 age group are shown in Table 1-2.

RACE& ETHNICITY

Non-Hispanic whites had the highest incidence of melanoma among all races and ethnicities in both age groups (0.2 per 100,000 in the 0-9 age group and 1.4 per 100,000 in the 10-19 age group.) Hispanics had the next highest rate of 0.1 per 100,000 in the 0-9 age group and 0.2 per 100,000 in the 10-19 age group. Under age 20, there were 131 Hispanics, and 36 non-Hispanic Blacks diagnosed with melanoma between 2003 and 2008. Table 1-3 shows melanoma incidence by ethnicity/race and ten-year age group. Figure 1-2 compares the incidence rates among Hispanics, non-Hispanic Blacks, and non-Hispanics of other races. We found a positive association with increasing age and melanoma incidence in all racial and ethnic groups. When comparing the distribution of melanoma cases by race and ethnicity for the younger age groups (0-19) compared to

adults (20+), patterns seen in the younger age groups mirror those seen in adults (20+ years); although, there was a lower proportion of Hispanics (2% versus 5%, respectively) and non-Hispanic Blacks (0.5% versus 1.4%, respectively) who were diagnosed with melanoma in the adult population compared to the 0-19 age group.(Figure 1-3)

STAGE

Nearly one quarter of the melanoma cases had 'unknown' listed as the stage at diagnosis. Of the remaining cases that were coded, the 10-19 year old and 20+ age groups had a similar stage distribution. However, the youngest age group (ages 0-9) had statistically significantly more melanomas diagnosed in the late stages than the two older age groups (x^2 = 63.59; p<0.0001) as can be seen in Figure 1-5. Table 1-4 shows incidence of melanoma by sex, age group, and stage. In the youngest age group, 45% were early stage, 26% were late stages, and 29% were unknown or unstaged. For the 10-19 age group, 67% were diagnosed in the early stages, 12 % were late stages, and 21% were unknown or unstaged. Likewise, 68% of adult tumors were diagnosed in the early stages, 11% were late, and 21% were unknown or unstaged.

BRESLOW DEPTH

Breslow depth (measurement of horizontal invasion in millimeters) was collected as a site specific factor beginning in 2004 by SEER Registries; all other registries were

excluded from this portion of the analysis. Of the SEER Registries, 702 cases (1.8%) were not included because of coding discrepancies. Figure 1-4 shows Breslow depth by 20-year age groups and incidence rates are provided in Table 1-5. The distribution of melanoma by tumor depth was very similar between the 0-19 year old age group and the oldest age group (ages 80+). The youngest and oldest age groups had the highest proportion of melanoma with a depth greater than 4.00 mm – 19.9 % and 21.3 %, respectively. The youngest and oldest age groups also had the highest proportion of melanoma with a depth of 2.01 to 4.00 mm. The associations between age and Breslow depth were statistically significant ($x^2 = 22.3$; $p<0.0001$).

HISTOLOGY

The majority (54.6 %) of 0-19 year olds had a histologic subtype coded as 'Melanoma, Not Otherwise Specified (NOS).' (Figure 1-6) Superficial spreading melanoma was the second most common histology (31.6 %), with nodular melanoma next (6.5%). The distribution by histologic subtype was similar among children, adolescents, and adults for the most common subtypes. However, the incidence of lentigo maligna melanoma was much lower in children and adolescents compared to adults - 0.6 % versus 5.9 %, respectively. (Table 1-6)

GENDER

Over the 1999-2008 timeframe, there were 50 melanomas diagnosed in males under the age of 1 (0.3 per 100,000) compared to 32 females (0.2 per 100,000). (See Figure 1-7) Incidence decreased slightly in the next age groups through age 9 where both males and females had an incidence of 0.1 per 100,000. Gender differences appear in the '10-14 years' age group where females have an age-specific incidence rate of 0.4 per 100,000 compared to 0.3 per 100,000 in males (Table 1-7). Incidence rates in females increased consistently with age with a statistically significant rise from 2.0 per 100,000 in the 15-19 year age group to 5.9 per 100,000 in the 20-24 age group ($p < 0.001$), after which the incidence in females began to diverge from that of males. Although rates increased consistently as age increased, the largest statistically significant increase in incidence for females occurred when rates rose from 27.9 per 100,000 in the 60-64 age group to 32.5 per 100,000 in the 65-69 age group. Incidence in males also increased consistently with age, although less rapidly than females for ages 15 through 44. The largest statistically significant jump in male incidence rates occurred between 70-74 years (87.5 per 100,000) and 75-79 years (105.0 per 100,000). In terms of relative incidence by gender, females showed a predominance as early as age 5 with a female-to-male rate ratio of 1.15, peaking in the 20-24 year old age group with a rate ratio of 2.34. By age 60, males developed melanoma at twice the rate of females (Figure 1-8).

Female predominance in melanoma incidence in the younger age groups was also depicted in race and ethnicity analyses for the 2003-2008 time period.(Table 1-8) In the 0-19 age group, Hispanics had a female-to-male rate ratio of 1.8 (95% CI: 1.2 – 2.6). Non-Hispanic blacks demonstrated similar patterns, although the rate ratio was not significant. As expected, the older age groups (20+) showed that melanoma incidence in males was higher than females after age group 40-44. The rate ratio for females-to-males in Hispanics was 0.9 (95% CI: 0.9 – 1.0). Non-Hispanic blacks had a rate ratio of 0.7 (95% CI: 0.7-0.7).

Time Trends

Over the ten year period, trends for 0-9 years, 10-19 years, 20-29 years, 30-39 years remained level.(Table 1-9) Significant increasing trends were seen in every age group beginning with 40-49 years ($p<0.05$). Males experienced a statistically significant decrease in incidence over time in the 20-29 age group (APC= -1.9, p=0.0). After 59, males experienced statistically significant increases in incidence over time.

DISCUSSION

Despite the increasing incidence of childhood melanoma, population-based data analyses characterizing childhood melanoma are lacking. The CINA Deluxe dataset available from NAACCR is a compilation of data from population-based cancer registries

nationwide and provided the largest compilation of high-quality data on melanoma cases for this comprehensive analysis of childhood and adolescent melanoma compared to adults.

Trends indicate that melanoma incidence in the youngest age groups is increasing, although not statistically significantly. In adolescent males there has been a statistically significant decrease in melanoma incidence, whereas a slight increase was seen in females of the same age over the ten year period.

Stage at diagnosis and Breslow depth at diagnosis were significantly different among children, adolescents, and adults (x^2 = 63.59; p<.0001). More than double the proportion of children ages 0-9 (26%) were diagnosed in the late stages of disease compared to adolescents ages 10-19 (12%) and adults ages 20 and older (11%.) Between 20 and 30 percent of melanomas were unstaged or unknown stage in each age group, indicating that the percentage of melanomas diagnosed in the later, more deadly stages is possibly even higher. Additionally, children and adolescents consistently had thicker tumors than adults; 31.2 percent of 0-19 year olds have a Breslow depth greater than 2 mm compared to 21.3 percent of adults.

There are several possible explanations why the children are being diagnosed at later stages. Most individuals who are ages 0-9 are likely to be under the care of a physician so that vaccination schedules and school physical exam requirements are met, so it is possible that initial misdiagnosis or delay in diagnosis is responsible for melanoma not being diagnosed in the early stages.[22-24] Up to 60 percent of patients being misdiagnosed have been reported in the literature. We thought that the histologies of melanoma tumors diagnosed in children may be different than those of adults, possibly explaining the difference in stage and Breslow depth. It is possible that there is a shorter latency for certain histologies, rather than a decade or more as previously thought.[25] However, nearly half of the childhood and adolescent cases did not have a specific histology code and patterns were difficult to evaluate. Of the coded cases, superficial spreading melanoma was the most common (31.6 %), followed by nodular melanoma (6.5%) which was similar to the distribution seen in adults. However, the relative frequency of lentigo maligna melanoma was much lower in children and adolescents compared to adults - 0.6 % versus 5.9 % respectively.

Differences in gender in adults have been discussed in the literature[26,27] and this study sought to establish when and if gender differences occurred in the youngest age groups. Although there was a higher incidence of melanoma in males under age one, differences in incidence by gender were not apparent for ages one through nine. Previous reports have demonstrated gender differences occurring beginning at age 15; however, our

analysis shows that gender differences start as early as age 10 when female incidence begins to surpass that of males. Rate ratios were statistically different by gender ($p < 0.05$) for every age group beginning at age 15.

The bimodal peak during child-bearing years and the onset of menopause suggests a relationship between hormonal/reproductive factors and melanoma incidence[28]; although published evidence is inconclusive. Lea et al. found in a case control study that oral contraceptive use and hormone replacement therapy were not associated with melanoma risk. However, they did find a positive association with more than two live births and melanoma risk (OR=3.3, $p<0.001$) in women younger than 55 years.[29] According to a recent review of all the controlled studies to date, Gupta et al.[30] found that evidence to date has not supported a potential role for hormonal/reproductive factors in melanoma. Alternatively, De Giorgi et al. found that estrogen receptors (particularly ER[beta]Î²) are an important factor in MM progression in recent immunohistochemical studies.[31]

Another plausible explanation for the increase in incidence in females between the 10-14 and 15-19 age groups is an increase in melanomas related to sun exposure. To explore this theory further we compared the relative frequency distribution in age 0-9 and ages 10-19 by anatomic site. We found that melanoma in children was more likely to be on the head & neck and limbs ($x^2=6.31$, $p=0.17$). Not until age 10 did the trunk

become the predominant anatomic site for males and females (x^2=2.87, p=0.09), continuing through adulthood. Further research is needed to elucidate the mechanisms underlying the role of gender.

Children and adolescents (0-19 years old) with melanoma were slightly more racially and ethnically diverse compared to adults. There was a higher proportion of Hispanic children and adolescents diagnosed with melanoma than adults (5.0 % versus 2.0 %, respectively); likewise, more non-Hispanic blacks were diagnosed in the youngest age groups compared to adults (1.4 % versus 0.5 %, respectively.) Non-Hispanics of other races also had a higher proportion of individuals diagnosed in the younger age groups compared to the older groups (6.6 % versus 4.6%.) This is consistent with SEER data analyzed by Hamre et al.[16] where they found that, compared to adult melanoma cases, there was a lower proportion of Caucasian patients under age 20. That people of non-white race and/or ethnicity have a greater incidence of melanoma during childhood and adolescence is compatible with the premise that non-environmental factors may be responsible for melanoma development during early life. Solar/ultraviolet exposure either is more causative in later life and/or takes many years of latency or exposure to result in melanoma.[25]

A limitation of this study was the imprecise coding of certain variables. As coding schema for neoplasms has become more complex, many cancer registries have found

that hospitals are using less descriptive, general codes in order to decrease abstraction time. In this case, we found that 98 to 99 percent of the cases had a microscopic confirmation with positive histology to diagnose the melanoma tumor. However, more than half of the cases (54.6 % of 0-19 year olds) had a non-specific histology code (Melanoma, not otherwise specified). Each histologic subtype characterizes melanoma differently and is important for studying epidemiologic trends.

CONCLUSION

In conclusion, melanoma incidence in children is significantly different than adults by stage, Breslow depth, race, ethnicity, and gender. This study adds valuable epidemiologic information for the youngest age groups; however, more research is necessary to learn why these differences are occurring. Increased awareness of melanoma in children is necessary to improve outcomes.

TABLE 1-1: POPULATION-BASED STUDIES FOR CHILDHOOD MELANOMA

Study	Country; Data Source	Study type	Years	Ages	Sample Size (# youngest)
Karlsson et al., 1998[32]	Sweden; Swedish National Cancer Registry	Descriptive	1973-92	0-19	177 (2 under 12)
Berg & Lindelof, 1997[33]	Sweden; Swedish National Cancer Registry	Descriptive	1958-1992	<21	287 (43 under 14)
Whiteman et al., 1997[14]	Queensland, Australia; Queensland Cancer Registry	Population-based case-control study	1987-1994	<15	61
Whiteman et al., 1995[13]	Queensland, Australia; Australian Paediatric Cancer Registry	Descriptive	1987-1994	<15	69
McWhirter & Dobson, 1995[12]	Australia Australian Paediatric Cancer Registry	Descriptive	1977-1989	<15	217
Strouse et al., 2005[15]	United States; SEER	Descriptive	1973-2001	<20	1051 (95 under 10)
Sander et al., 1999[9]	Sweden; Swedish National Cancer Registry	Descriptive	1973-1992	<20	177
Hamre et al., 2002[16]	United States; SEER	Descriptive	1973-1996	<20	698
Wu et al., 2005[17]	United States; NAACCR	Descriptive	1995-1999	15-49	304,668
Conti et al., 2000[34]	Europe; EUROCARE	Descriptive	1978-1989	<15	204 (93 under 10)

SEER= Surveillance, Epidemiology and End Results Program, National Cancer Institute; NAACCR = North American Association of Central Cancer Registries

TABLE 1-2: MELANOMA INCIDENCE IN CHILDREN AND ADOLESCENTS* BY GENDER AND ANATOMIC SITE, 1995-2008

GENDER	SITE	FREQUENCY	RATE	95% CI
Male	Head & Neck	577	0.12	(0.11 - 0.13)
	Trunk	779	0.16	(0.15 - 0.18)
	Upper limb & shoulder	345	0.07	(0.07 - 0.08)
	Lower limb & hip	265	0.06	(0.05 - 0.06)
	Site not otherwise specified	70	0.01	(0.01 – 0.02)
Female	Head & Neck	440	0.10	(0.09 - 0.11)
	Trunk	1031	0.23	(0.22 - 0.24)
	Upper limb & shoulder	536	0.12	(0.11 - 0.13)
	Lower limb & hip	751	0.17	(0.16 - 0.18)
	Site not otherwise specified	51	0.01	(0.01 – 0.01)

Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. Rates are per 100,000 and age-adjusted to the 2000 US Standard Population; CI: 95% Confidence intervals.
*Ages 0 to19 are considered children and adolescents.

TABLE 1-3: MELANOMA INCIDENCE BY RACE/ETHNICITY AND AGE, 2003-2008

AGE GROUP		COUNT	RATE	95% CI
00-09 years				
	Hispanic	31	0.1	0.0 - 0.1
	NHW	255	0.2	0.2 - 0.2
	NHB	15	0	0.0 - 0.1
	NHO	12	0.1	0.0 - 0.2
10-19 years				
	Hispanic	100	0.2	0.2 - 0.3
	NHW	2,013	1.4	1.3 - 1.4
	NHB	21	0.1	0.0 - 0.1
	NHO	22	0.2	0.1 - 0.3
20-29 years				
	Hispanic	390	0.9	0.8 - 1.0
	NHW	11,545	8.2	8.1 - 8.4
	NHB	59	0.2	0.1 - 0.2
	NHO	119	0.8	0.7 - 1.0
30-39 years				
	Hispanic	957	2.4	2.2 - 2.5
	NHW	22,818	15.9	15.7 - 16.2
	NHB	109	0.4	0.3 - 0.5
	NHO	239	1.5	1.3 - 1.7
40-49 years				
	Hispanic	1,323	4.2	4.0 - 4.5
	NHW	43,287	24.5	24.3 - 24.7
	NHB	206	0.7	0.6 - 0.8
	NHO	343	2.5	2.2 - 2.7
50-59 years				
	Hispanic	1,205	6.3	6.0 - 6.7
	NHW	58,186	36.5	36.2 - 36.8
	NHB	252	1.1	1.0 - 1.3
	NHO	366	3.4	3.1 - 3.8
60-69 years				
	Hispanic	1,089	10.7	10.1 - 11.4
	NHW	58,269	56	55.6 - 56.5
	NHB	318	2.6	2.3 - 2.9
	NHO	364	6.1	5.5 - 6.8
70-79 years				
	Hispanic	997	16.7	15.7 - 17.7
	NHW	56,701	77.4	76.7 - 78.0
	NHB	344	4.5	4.0 - 5.0
	NHO	286	8.3	7.4 - 9.3
80+ years				
	Hispanic	635	20.6	19.0 - 22.2
	NHW	40,537	79.8	79.0 - 80.5
	NHB	309	7.6	6.8 - 8.5
	NHO	187	10.6	9.1 - 12.2

Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. Rates are per 100,000, age-adjusted to 2000 US Std Pop; CI: 95% Confidence intervals

TABLE 1-4: MELANOMA INCIDENCE BY GENDER, STAGE, AND 10-YEAR AGE GROUPS, 2003-2008

AGE		MALE AND FEMALE			MALE			FEMALE		
GROUP	STAGE	COUNT	RATE	95% CI	COUNT	RATE	95% CI	COUNT	RATE	95% CI
00-09 yr	Early	151	0.1	0.1 - 0.1	72	0.1	0.0 - 0.1	79	0.1	0.1 - 0.1
	Late	87	0	0.0 - .00	44	0	0.0 - 0.1	43	0	0.0 - 0.1
	Unk/Uns	99	0	0.0 - 0.1	57	0	0.0 - 0.1	42	0	0.0 - 0.1
10-19 yr	Early	1,540	0.7	0.6 - 0.7	577	0.5	0.4 - 0.5	963	0.8	0.8 - 0.9
	Late	282	0.1	0.1 - 0.1	147	0.1	0.1 - 0.1	135	0.1	0.1 - 0.1
	Unk/Uns	488	0.2	0.2 - 0.2	196	0.2	0.1 - 0.2	292	0.3	0.2 - 0.3
20-29 yr	Early	9,243	4	3.9 - 4.1	2,687	2.3	2.2 - 2.4	6,556	5.8	5.7 - 6.0
	Late	1,174	0.5	0.5 - 0.5	601	0.5	0.5 - 0.6	573	0.5	0.5 - 0.6
	Unk/Uns	2,662	1.2	1.1 - 1.2	838	0.7	0.7 - 0.8	1,824	1.6	1.5 - 1.7
30-39 yr	Early	18,755	8.2	8.1 - 8.4	7,135	6.2	6.1 - 6.4	11,620	10.3	10.1 - 10.5
	Late	2,370	1	1.0 - 1.1	1,275	1.1	1.1 - 1.2	1,095	1	0.9 - 1.0
	Unk/Uns	4,940	2.2	2.1 - 2.2	1,912	1.7	1.6 - 1.7	3,028	2.7	2.6 - 2.8
40-49 yr	Early	34,400	13.6	13.5 - 13.8	15,594	12.4	12.2 - 12.6	18,806	14.8	14.6 - 15.1
	Late	4,836	1.9	1.9 - 2.0	2,965	2.4	2.3 - 2.5	1,871	1.5	1.4 - 1.5
	Unk/Uns	9,534	3.8	3.7 - 3.9	4,596	3.7	3.6 - 3.8	4,938	3.9	3.8 - 4.0
50-59 yr	Early	44,710	21.1	20.9 - 21.3	25,372	24.5	24.2 - 24.8	19,338	17.9	17.7 - 18.2
	Late	7,139	3.4	3.3 - 3.5	4,735	4.6	4.5 - 4.7	2,404	2.2	2.1 - 2.3
	Unk/Uns	12,876	6.1	6.0 - 6.2	7,636	7.4	7.2 - 7.6	5,240	4.8	4.7 - 5.0
60-69 yr	Early	44,020	33.2	32.9 - 33.6	28,453	45.7	45.1 - 46.2	15,567	22.2	21.9 - 22.6
	Late	7,266	5.5	5.4 - 5.6	4,993	8	7.8 - 8.2	2,273	3.2	3.1 - 3.4
	Unk/Uns	13,311	10.1	9.9 - 10.2	8,680	13.9	13.6 - 14.2	4,631	6.6	6.4 - 6.8
70-79 yr	Early	41,670	46.1	45.7 - 46.6	27,702	70.3	69.5 - 71.2	13,968	27.4	27.0 - 27.9
	Late	7,404	8.2	8.0 - 8.4	5,022	12.8	12.4 - 13.1	2,382	4.7	4.5 - 4.9
	Unk/Uns	13,184	14.6	14.3 - 14.8	8,866	22.5	22.0 - 23.0	4,318	8.5	8.2 - 8.7
80+ yr	Early	28,582	47.8	47.3 - 48.4	17,699	84.9	83.7 - 86.2	10,883	28	27.5 - 28.6
	Late	5,886	9.8	9.6 - 10.1	3,610	17.4	16.9 - 18.0	2,276	5.8	5.6 - 6.1
	Unk/Uns	9,994	16.7	16.4 - 17.0	6,072	29.3	28.5 - 30.0	3,922	10.1	9.7 - 10.4

Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. Rates are per 100,000 and age-adjusted to the 2000 US Std Population standard. CI: 95% Confidence intervals (Tiwari mod). Unk/Uns= unknown or unstaged.

TABLE 1-5: MELANOMA INCIDENCE IN CHILDREN & ADOLESCENTS COMPARED TO ADULTS BY BRESLOW DEPTH, 20-YEAR AGE GROUPS, 2004-2008

AGE GROUPS	BRESLOW DEPTH (MM)	COUNT	RATE	95% CI
0-19 years	0.01-1.00	154	0.3	0.2 - 0.3
	1.01-2.00	47	0.1	0.1 - 0.1
	2.01-4.00	33	0.1	0.0 - 0.1
	4.01+	58	0.1	0.1 - 0.1
20-39 years				
	0.01-1.00	3,655	6.4	6.1 - 6.6
	1.01-2.00	573	1	0.9 - 1.1
	2.01-4.00	232	0.4	0.4 - 0.5
	4.01+	507	0.9	0.8 - 1.0
40-59 years				
	0.01-1.00	9,816	17.2	16.8 - 17.5
	1.01-2.00	1,791	3.1	3.0 - 3.3
	2.01-4.00	831	1.4	1.3 - 1.5
	4.01+	1,636	2.8	2.7 - 3.0
60-79 years				
	0.01-1.00	9,227	37.9	37.1 - 38.6
	1.01-2.00	1,930	8	7.6 - 8.4
	2.01-4.00	1,193	5	4.7 - 5.3
	4.01+	2,054	8.6	8.2 - 8.9
80+ years				
	0.01-1.00	2,748	40.7	39.2 - 42.3
	1.01-2.00	792	11.7	10.9 - 12.6
	2.01-4.00	688	10.2	9.4 - 11.0
	4.01+	1,146	16.9	15.9 - 17.9

Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. Rates are per 100,000 and age-adjusted to the 2000 US Std Population standard. CI: 95% Confidence intervals (Tiwari mod).NOTE: Based on SEER Registries only.

TABLE 1-6: MELANOMA INCIDENCE FOR CHILDREN & ADOLESCENTS COMPARED TO ADULTS FOR HISTOLOGIC SUBTYPE, 2003-2008

HISTOLOGIC SUBTYPES	0-19 YEARS COUNT	(%)	20 + YEARS COUNT	(%)
NOS	1,424	(54.6)	169,619	(54.0)
Superficial spreading	825	(31.6)	86,934	(27.7)
Nodular	170	(6.5)	21,737	(6.9)
Lentigo maligna	15	(0.6)	18,561	(5.9)
Spindle cell melanoma	23	(0.9)	3,636	(1.2)
Desmoplastic melanoma	7	(0.3)	3,580	(1.1)
Acral lentiginous	18	(0.7)	3,033	(1.0)
In giant pigmented nevus	43	(1.6)	904	(0.3)
Mixed (epithelioid & spindle cell)	42	(1.6)	715	(0.2)
Other	41	(1.6)	5,320	(1.7)

Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program.

TABLE 1-7: MELANOMA INCIDENCE IN CHILDREN & ADOLESCENTS COMPARED WITH ADULTS BY 5-YEAR AGE GROUP AND GENDER, 1999-2008

5 YR AGE GROUP	GENDER	COUNT	RATE	95% CI	RATE RATIO	95% CI FOR RATE RATIO
< 01 years	Male	50	0.3	0.2 - 0.4		
	Female	32	0.2	0.1 - 0.3	0.67	0.42 - 1.07
01-04 years	Male	55	0.1	0.1 - 0.1		
	Female	49	0.1	0.1 - 0.1	0.93	0.62 - 1.39
05-09 years	Male	101	0.1	0.1 - 0.2		
	Female	111	0.1	0.1 - 0.2	1.15	0.87 - 1.52
10-14 years	Male	290	0.3	0.3 - 0.4		
	Female	300	0.4	0.3 - 0.4	1.09	0.92 - 1.28
15-19 years	Male	1,026	1.2	1.2 - 1.3		
	Female	1,614	2	1.9 - 2.2	1.67*	1.54 - 1.80
20-24 years	Male	2,058	2.5	2.4 - 2.6		
	Female	4,546	5.9	5.7 - 6.1	2.34*	2.22 - 2.46
25-29 years	Male	3,629	4.6	4.5 - 4.8		
	Female	7,175	9.5	9.3 - 9.7	2.06*	1.98 - 2.14
30-34 years	Male	5,715	7.2	7.0 - 7.4		
	Female	9,524	12.3	12.1 - 12.6	1.71*	1.66 - 1.77
35-39 years	Male	8,874	10.6	10.4 - 10.8		
	Female	12,402	14.9	14.7 - 15.2	1.41*	1.37 - 1.45
40-44 years	Male	13,403	15.5	15.2 - 15.7		
	Female	16,012	18.3	18.1 - 18.6	1.19*	1.16 - 1.21
45-49 years	Male	18,136	21.9	21.6 - 22.2		
	Female	17,830	21	20.7 - 21.3	0.96*	0.94 - 0.98
50-54 years	Male	22,350	30.5	30.1 - 30.9		
	Female	17,624	23.2	22.8 - 23.5	0.76*	0.74 - 0.77
55-59 years	Male	25,077	41.9	41.4 - 42.4		
	Female	15,843	25	24.6 - 25.4	0.60*	0.58 - 0.61
60-64 years	Male	25,192	54.9	54.3 - 55.6		
	Female	13,997	27.9	27.4 - 28.4	0.51*	0.50 - 0.52
65-69 years	Male	25,825	71.6	70.7 - 72.4		
	Female	13,448	32.5	31.9 - 33.0	0.45*	0.44 - 0.46
70-74 years	Male	26,455	87.5	86.5 - 88.6		
	Female	13,372	35.9	35.2 - 36.5	0.41*	0.40 - 0.42
75-79 years	Male	25,664	105	103.7 - 106.3		
	Female	13,298	39.6	38.9 - 40.2	0.38*	0.37 - 0.38
80-84 years	Male	19,169	117.6	115.9 - 119.2		
	Female	10,713	41	40.2 - 41.7	0.35*	0.34 - 0.36
85+ years	Male	13,610	121.8	119.7 - 123.8		
	Female	10,083	39.5	38.7 - 40.3	0.32*	0.31 - 0.33

Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. Rates are per 100,000; CI: Confidence intervals are 95% for rates and ratios.

*The rate ratio indicates that the rate is significantly different than the rate for Male ($p<0.05$).

TABLE 1-8: MELANOMA INCIDENCE IN CHILDREN & ADOLESCENTS COMPARED TO ADULTS BY RACE, ETHNICITY, AND GENDER, 2003-2008

ETHNICITY / RACE	GENDER	AGES 0-19					AGES 20+				
		COUNT	RATE	95% CI	RR	95% CI RR	COUNT	RATE	95% CI	RR	95% CI RR
Hisp	M	49	0.1	(0.1 - 0.1)			2,955	6.5	(6.2 - 6.7)		
	F	82	0.2	(0.2 - 0.2)	1.8*	(1.2 - 2.6)	3,641	5.9	(5.7 - 6.1)	0.9*	(0.9 - 1.0)
NHW	M	927	0.6	(0.6 - 0.7)			168,604	39.6	(39.4 - 39.8)		
	F	1,341	1.0	(0.9 - 1.0)	1.5*	(1.4 - 1.6)	122,739	26.2	(26.0 - 26.3)	0.7*	(0.7 - 0.7)
NHB	M	15	0.0	(0.0 - 0.1)			676	1.6	(1.4 - 1.7)		
	F	21	0.1	(0.0 - 0.1)	1.4	(0.7 - 2.9)	921	1.4	(1.3 - 1.5)	0.9*	(0.8 - 1.0)

Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. Rates are per 100,000 and age-adjusted to the 2000 US Std Population; CI: Confidence intervals (Tiwari mod) are 95% for rates and ratios.

* The rate ratio (RR) indicates that the female rate is significantly different than the male rate ($p<0.05$).

TABLE 1-9: ANNUAL PERCENT CHANGES (APC) IN MELANOMA INCIDENCE FOR CHILDREN & ADOLESCENTS COMPARED TO ADULTS BY GENDER, 1999-2008

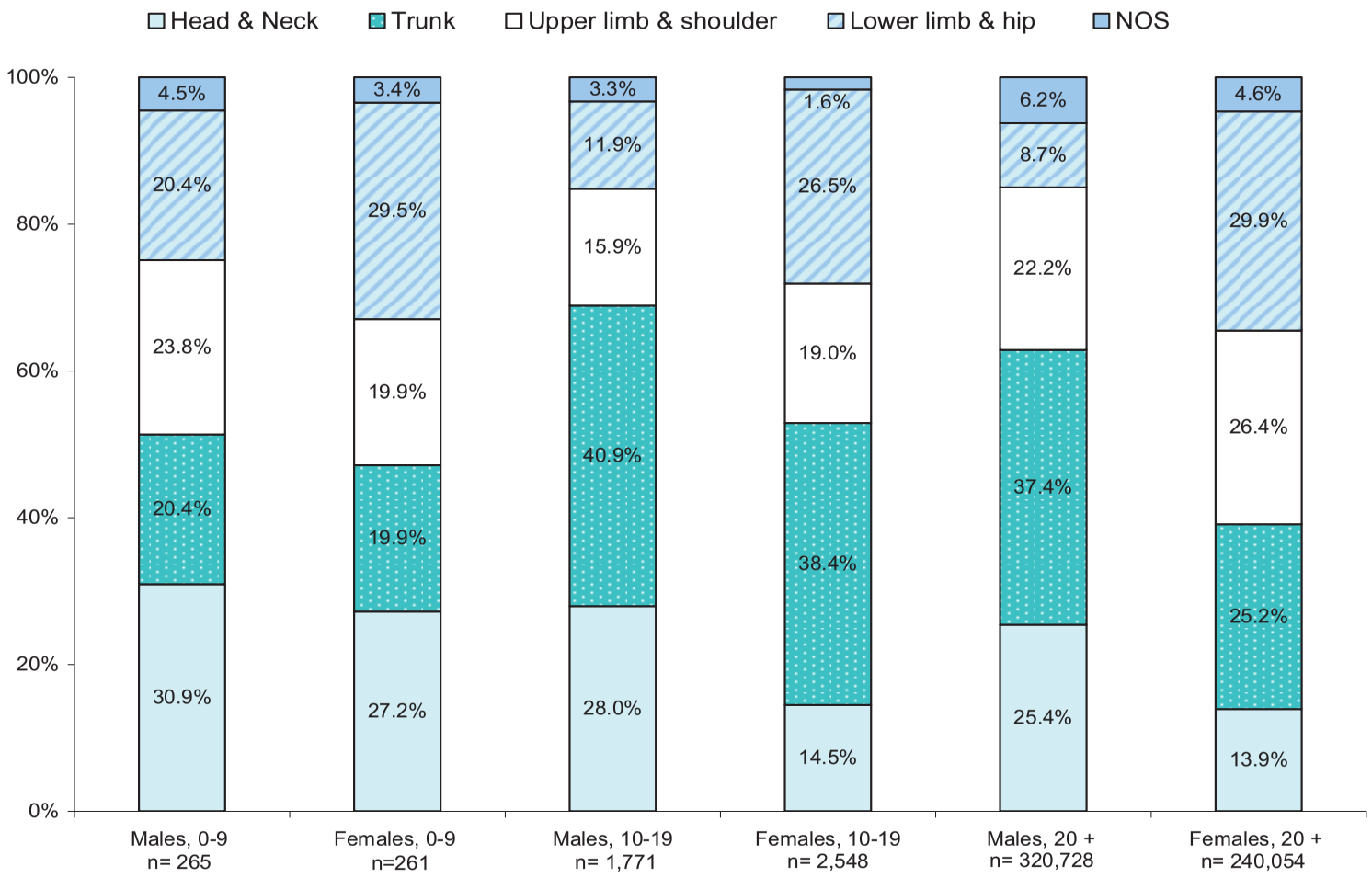
	Males			Females		
	APC	P-value	95% CI	APC	P-value	95% CI
00-09 years	5.2	0.1	-2.2 - 13.1	6.3	0.2	-2.9 - 16.4
10-19 years	-2.0	0.4	-6.7 - 2.8	0.8	0.6	-2.5 - 4.1
20-29 years	-1.9*	0	-3.5 - -0.2	1.8	0.1	-0.1 - 3.7
30-39 years	-0.8	0.2	-2.3 - 0.6	1.2	0.1	-0.2 - 2.7
40-49 years	-0.4	0.3	-1.3 - 0.5	1.9*	0	0.4 - 3.4
50-59 years	0.9	0.1	0.0 - 1.8	2.7*	0	1.6 - 3.7
60-69 years	2.6*	0	1.7 - 3.4	3.1*	0	2.2 - 3.9
70-79 years	3.5*	0	2.6 - 4.4	2.7*	0	1.4 - 3.9
80+ years	4.1*	0	3.5 - 4.7	3.1*	0	2.5 - 3.7

Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. CI: Confidence intervals are 95% for rates (Tiwari mod) and trends.

Percent changes were calculated using 1 year for each end point; APCs were calculated using weighted least squares method.

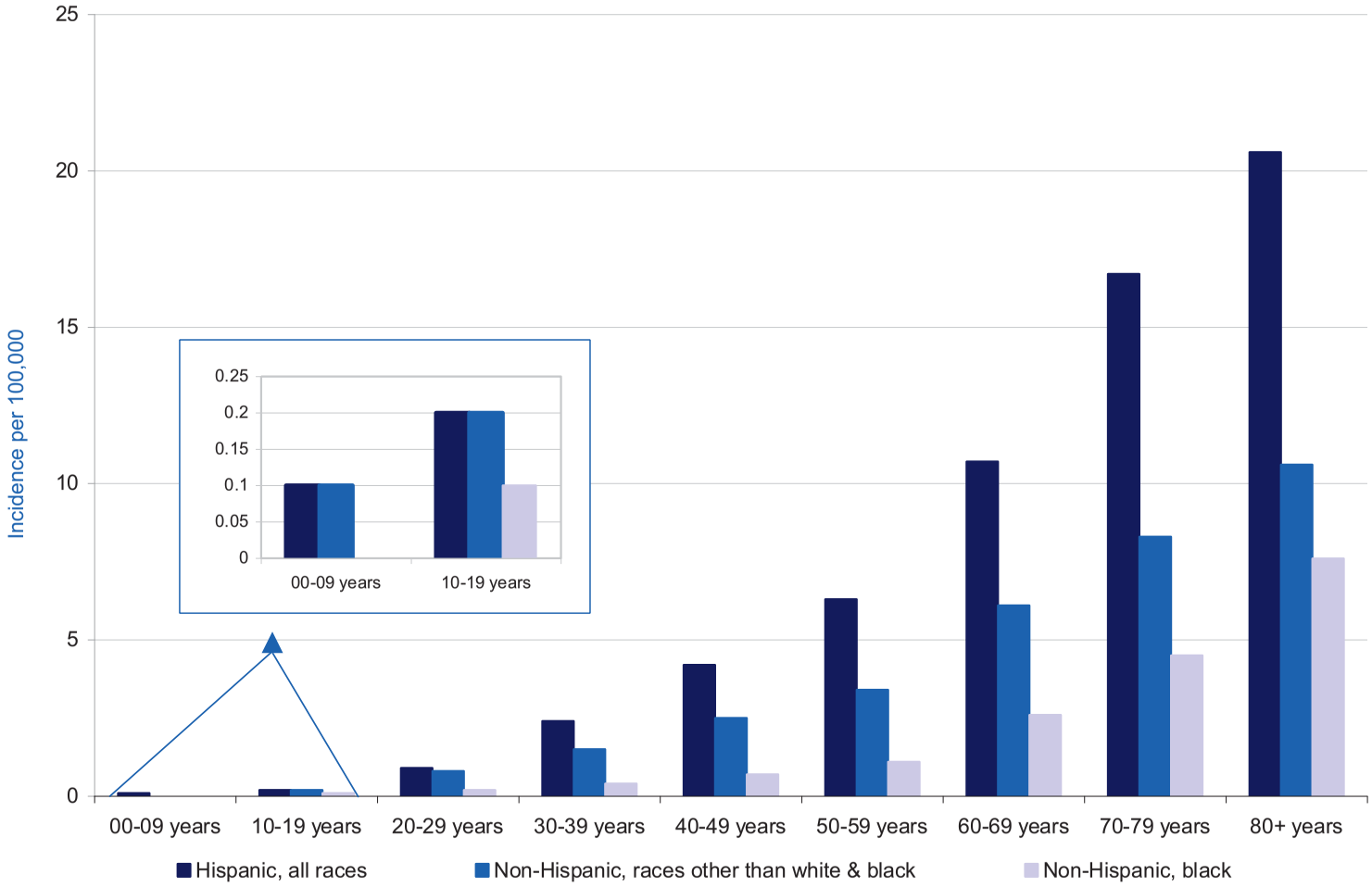
* The APC is significantly different from zero ($p<0.05$).

FIGURE 1-1: RELATIVE FREQUENCY DISTRIBUTIONS OF MELANOMA DIAGNOSED IN CHILDREN (AGE ≤9), ADOLESCENTS (AGE 10-19), AND ADULTS (AGE 20+), ANATOMIC SITE, AND GENDER, 1995-2008



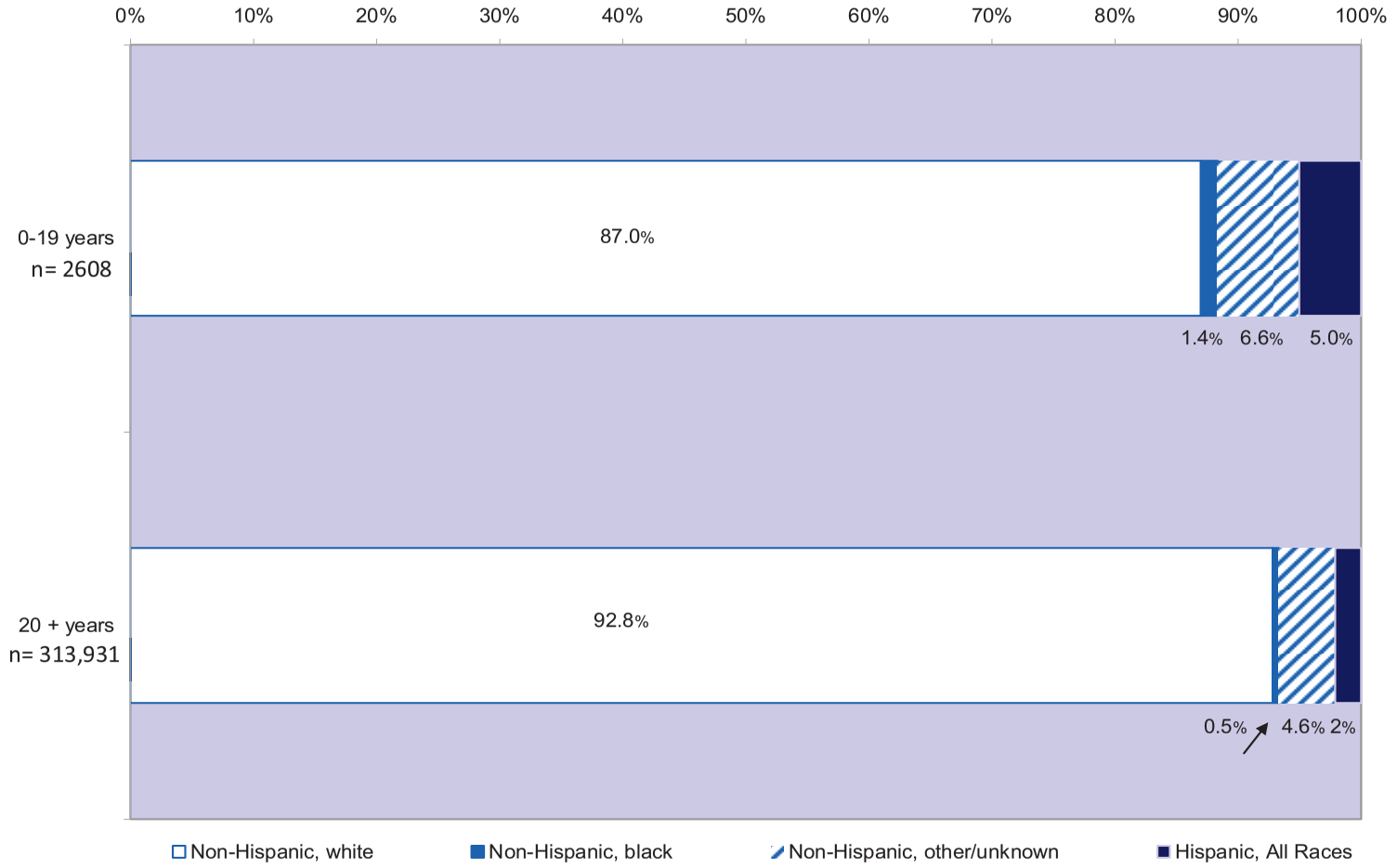
Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. NOS= Not otherwise specified.

FIGURE 1-2 MELANOMA INCIDENCE RATES BY RACE & ETHNICITY AND 10-YEAR AGE GROUPS, 2003-2008



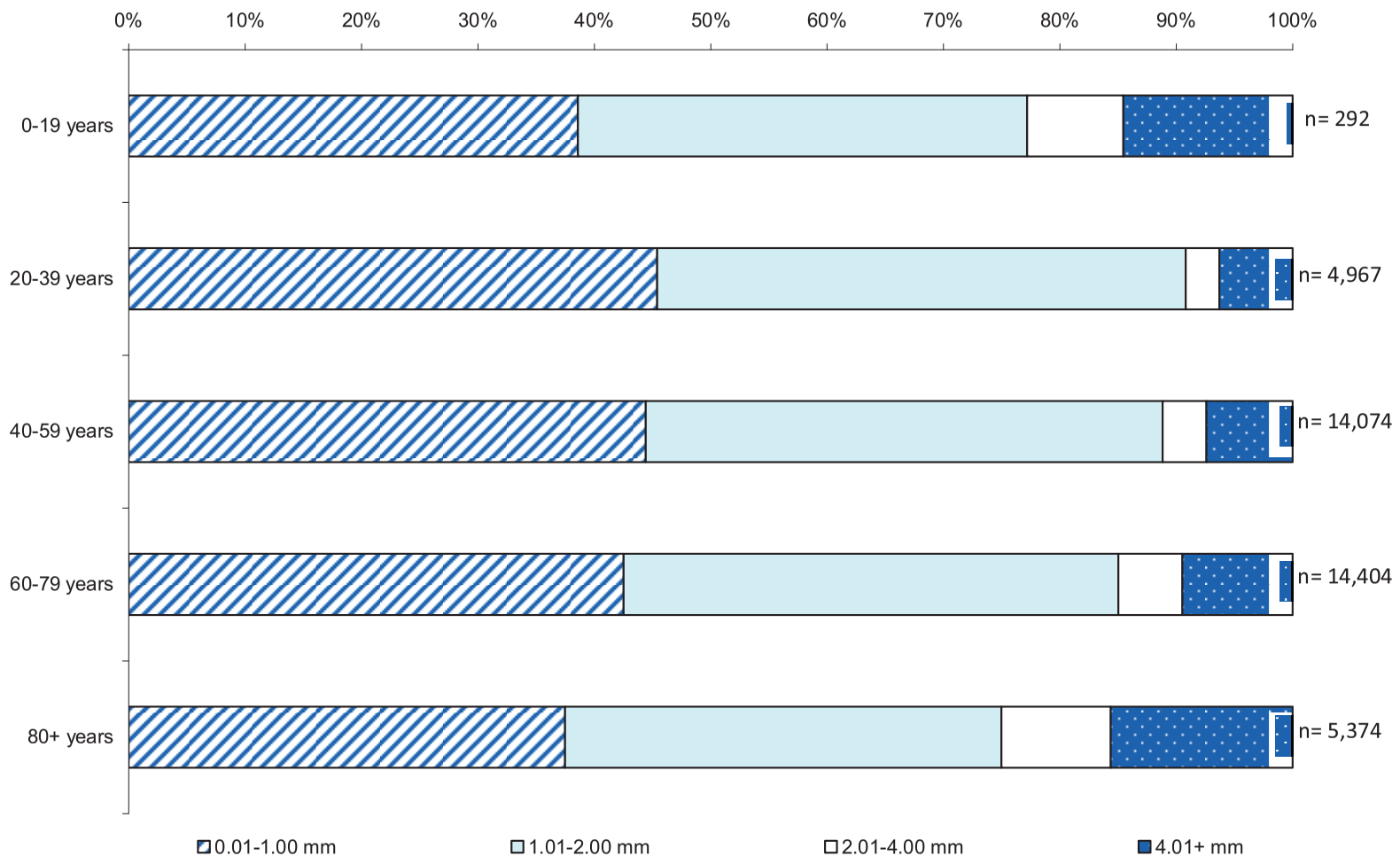
Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. Rates are per 100,000 and age-adjusted to the 2000 US Std Population NOTE: Race and ethnicity are not mutually exclusive.

FIGURE 1-3: RELATIVE FREQUENCY DISTRIBUTION OF MELANOMA DIAGNOSED BY RACE AND ETHNICITY, CHILDREN/ADOLESCENTS (AGE 0-19) COMPARED TO ADULTS (20+), 2003-2008



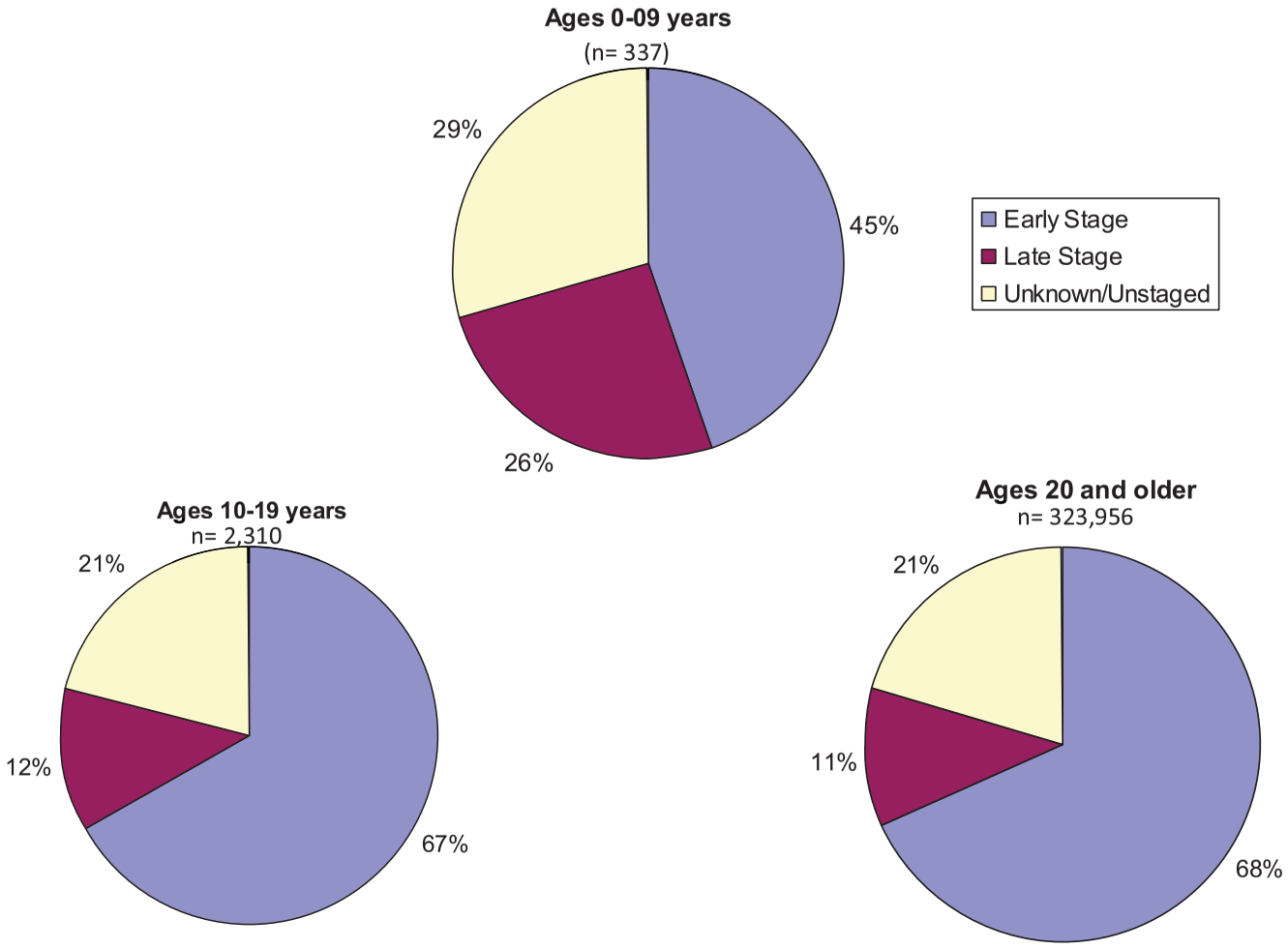
Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. NOTE: Race and ethnicity are not mutually exclusive.

FIGURE 1-4: RELATIVE FREQUENCY DISTRIBUTION OF MELANOMA BY BRESLOW DEPTH (MM) AND AGE GROUP 2004-2008



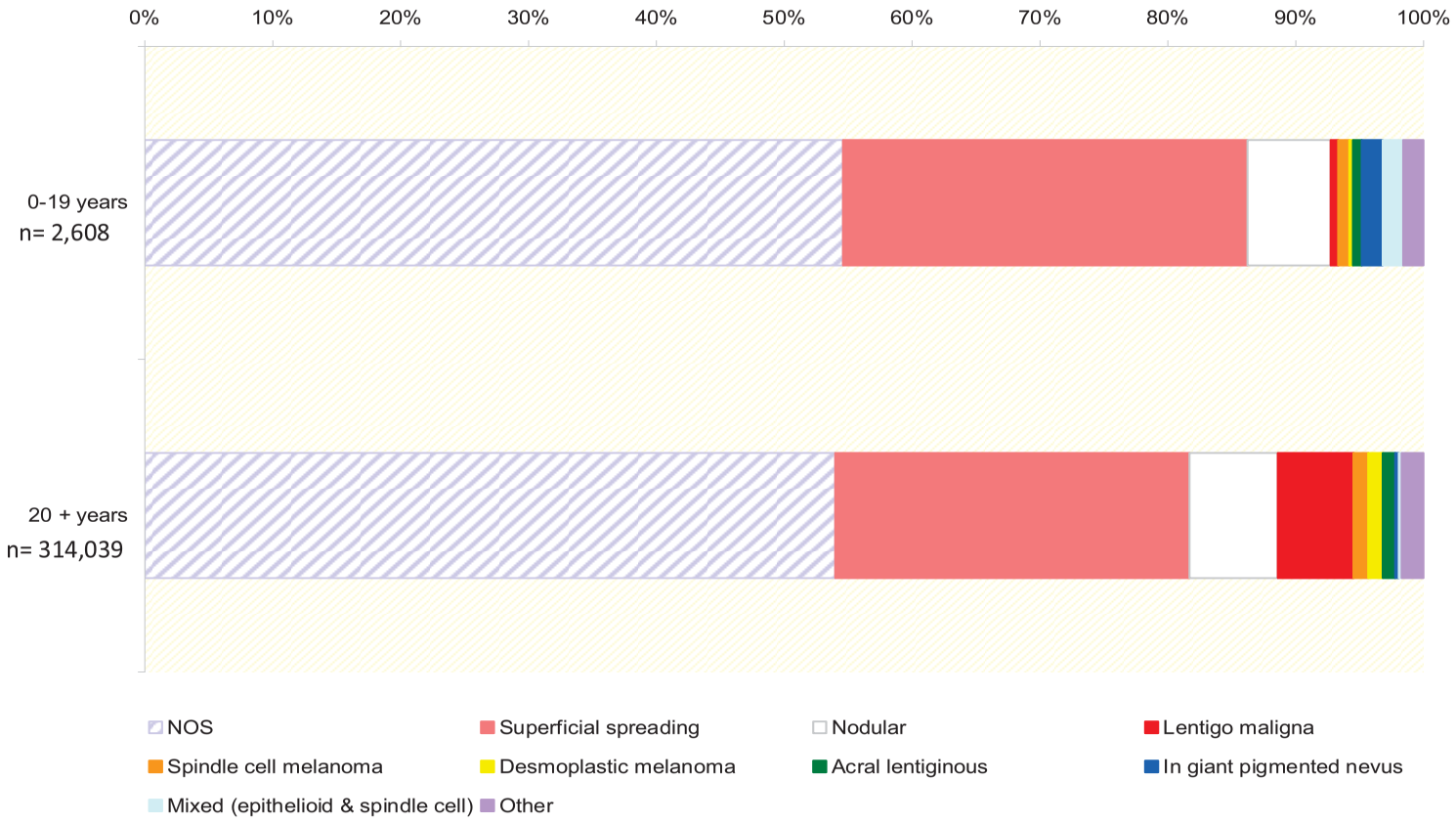
Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program.

FIGURE 1-5: RELATIVE FREQUENCY DISTRIBUTIONS OF MELANOMA BY STAGE AT DIAGNOSIS FOR CHILDREN (AGE≤9), ADOLESCENTS (AGE 10-19), AND ADULTS(AGE 20+), 2003-2008



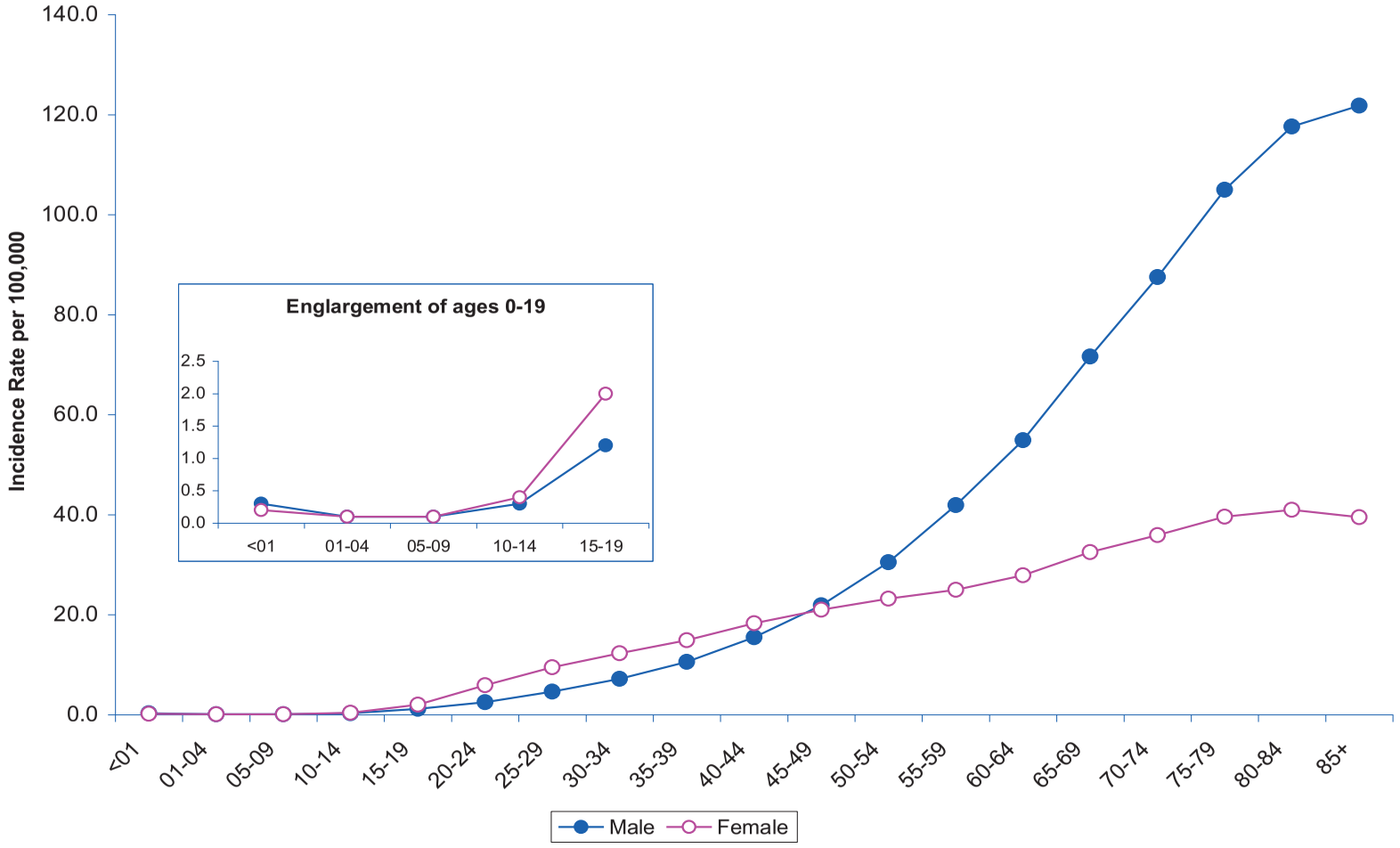
Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program.

FIGURE 1-6: RELATIVE FREQUENCY DISTRIBUTIONS OF MELANOMA IN CHILDREN/ADOLESCENTS (AGE 0-19) COMPARED TO ADULTS (AGE 20+) BY DISTRIBUTION OF HISTOLOGIC SUBTYPES, 2003-2008



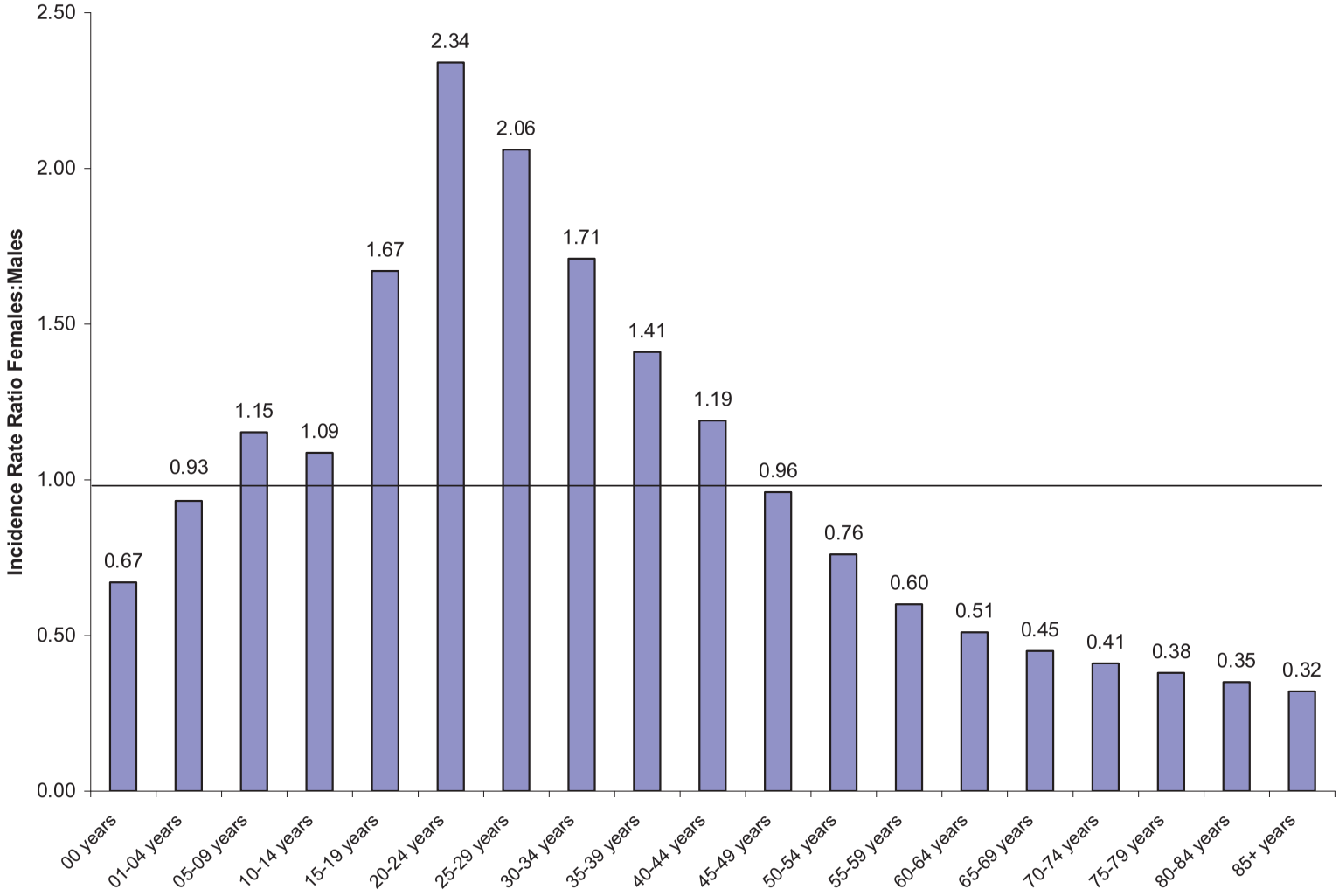
Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. NOS= Not otherwise specified.

FIGURE 1-7: MELANOMA INCIDENCE RATES BY GENDER AND 5-YEAR AGE GROUP, 1999-2008



Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program. Rates are per 100,000.

FIGURE 1-8: MELANOMA INCIDENCE RATE RATIOS (FEMALE:MALE) BY 5-YEAR AGE GROUP, 1999-2008



Source: NAACCR Incidence – CINA Analytic File, 1995-2008, for NHIAv2 Origin, Standard File, SEER*Stat Software Program.
Rates are per 100,000

REFERENCES

(1) American Cancer Society. Cancer Facts & Figures 2012. Atlanta, GA: American Cancer Society, 2012.

(2) Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg LX et al. SEER Cancer Statistics Review, 1975-2000. Bethesda, MD: National Cancer Institute, 2003.

(3) Wu SJ, Lambert DR. Melanoma in children and adolescents. Pediatric Dermatology 1997; 14(2):87-92.

(4) Ferrari A, Bono A, Baldi M, Collini P, Casanova M, Pennacchioli E et al. Does melanoma behave differently in younger children than in adults? A retrospective study of 33 cases of childhood melanoma from a single institution. Pediatrics 2005; 115 (3), 649-654.

(5) Ceballos PI, Ruiz-Maldonado R, Mihm MC, Jr. Melanoma in children. New England Journal of Medicine 1995; 332(10):656-662.

(6) Barnhill RL. Childhood melanoma. Seminars in Diagnostic Pathology 1998; 15(3):189-194.

(7) Roth ME, Grant-Kels JM, Kuhn MK, Greenberg RD, Hurwitz S. Melanoma in children. Journal of the American Academy of Dermatology 1990; 22(2 Pt 1):265-274.

(8) Ruiz-Maldonado R, Orozco-Covarrubias ML. Malignant melanoma in children. A review.[erratum appears in Arch Dermatol 1997 Jul;133(7):833]. Archives of Dermatology 1997; 133(3):363-371.

(9) Sander B, Karlsson P, Rosdahl I, Westermark P, Boeryd B. Cutaneous malignant melanoma in Swedish children and teenagers 1973-1992: a clinico-pathological study of 130 cases. International Journal of Cancer 1999; 80(5):646-651.

(10) Tate PS, Ronan SG, Feucht KA, Eng AM, Das G. Melanoma in childhood and adolescence: clinical and pathological features of 48 cases. Journal of Pediatric Surgery 1993; 28(2):217-222.

(11) Pearce MS, Parker L, Cotterill SJ, Gordon PM, Craft AW. Skin cancer in children and young adults: 28 years' experience from the Northern Region Young Person's Malignant Disease Registry, UK. Melanoma Research 2003; 13(4):421-426.

(12) McWhirter WR, Dobson C. Childhood melanoma in Australia. World Journal of Surgery 1995; 19(3):334-336.

(13) Whiteman D, Valery P, McWhirter W, Green A. Incidence of cutaneous childhood melanoma in Queensland, Australia. International Journal of Cancer 1995; 63(6):765-768.

(14) Whiteman DC, Valery P, McWhirter W, Green AC. Risk factors for childhood melanoma in Queensland, Australia. International Journal of Cancer 1997; 70(1):26-31.

(15) Strouse JJ, Fears TR, Tucker MA, Wayne AS. Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. Journal of Clinical Oncology 2005; 23(21):4735-4741.

(16) Hamre MR, Chuba P, Bakhshi S, Thomas R, Severson RK. Cutaneous melanoma in childhood and adolescence. Pediatric Hematology & Oncology 2002; 19(5):309-317.

(17) Wu X, Groves FD, McLaughlin CC, Jemal A, Martin J, Chen VW. Cancer incidence patterns among adolescents and young adults in the United States. Cancer Causes & Control 2005; 16(3):309-320.

(18) Surveillance,Epidemiology,and End Results (SEER) program. SEER*Stat database: populations--total U.S. 1969-2009. (www.seer.cancer.gov/popdata) Bethesda, MD:National Cancer Institute, DCCPS, Surveillance Research Program, 2012.

(19) Tiwari RCCLX, Zou Z. Efficient interval estimation for age-adjusted cancer rates. Stat Methods Med Res 2006; 15(6), 547-569.

(20) SEER Summary Staging Manual - 2000: Codes and Coding Instructions. NIH Pub No. 01-4969 ed. Bethesda, MD: National Cancer Institute, 2001.

(21) NAACCR Latino Research Work Group. NAACCR Guideline for Enhancing Hispanic/Latino Identification: Revised NAACCR Hispanic/Latino Identification Algorithm [NHIA v2]. Springfield, IL: North American Association of Central Cancer Registries, 2005.

(22) Pappo AS. Melanoma in children and adolescents. European Journal of Cancer 2003; 39(18):2651-2661.

(23) Melnik MK, Urdaneta LF, Al Jurf AS, Foucar E, Jochimsen PR, Soper RT. Malignant melanoma in childhood and adolescence. American Surgeon 1986; 52(3):142-147.

(24) Saenz NC, Saenz-Badillos J, Busam K, LaQuaglia MP, Corbally M, Brady MS . Childhood melanoma survival. Cancer 1999; 85(3):750-754.

(25) Herzog C, Pappo AS, Bondy M, Bleyer A, Kirkwood J. Malignant Melanoma. In: Bleyer A, O'Leary M, Barr R, Ries LAG, editors. Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age, Including SEER Incidence and Survival: 1975-2000. Bethesda, MD: National Cancer Institute, 2006: 54-63.

(26) Scoggins CRM, Ross MIM, Reintgen DSM+, Noyes RDM, Goydos JSM, Beitsch PDM et al. Gender-Related Differences in Outcome for Melanoma Patients. Annals of Surgery Scientific Papers of the 2006; 117th Annual Meeting of the Southern Surgical Association 2006; 243(5):693-700.

(27) Nieto. A, RuizRamos M, Abdel-Kader. L, Conde. M, Camacho. F. Gender differences in rising trends in cutaneous malignant melanoma in Spain, 1975-98. British Journal of Dermatology 2003; 148 (1), 110-116.

(28) Stoica A, Hoffman M, Marta L, Voiculetz N. Estradiol and progesterone receptors in human cutaneous melanoma. Neoplasma 1991; 38(2):137-145.

(29) Lea CS, Holly EA, Hartge P, Lee JS, Guerry D, Elder DE et al. Reproductive risk factors for cutaneous melanoma in women: a case-control study. American Journal of Epidemiology 2007; 165(5):505-513.

(30) Gupta A, Driscoll MS. Do hormones influence melanoma? Facts and controversies. Clinics in Dermatology 2010; 28(3):287-292.

(31) de Giorgi V, Gori A, Grazzini M, Rossari S, Scarfi F, Corciova S et al. Estrogens, estrogen receptors and melanoma. Expert Review of Anticancer Therapy 2011; 11(5):739-747.

(32) Karlsson P, Boeryd B, Sander B, Westermark P, Rosdahl I. Increasing incidence of cutaneous malignant melanoma in children and adolescents 12-19 years of age in Sweden 1973-92. Acta Dermato-Venereologica 1998; 78(4):289-292.

(33) Berg P, Lindelof B. Differences in malignant melanoma between children and adolescents. A 35-year epidemiological study. Archives of Dermatology 1997; 133(3):295-297.

(34) Conti EM, Cercato MC, Gatta G, Ramazzotti V, Roscioni S, EUROCARE Working Group. Childhood melanoma in Europe since 1978: a population-based survival study. European Journal of Cancer 2001; 37(6):780-784.

CHAPTER 2 : UNDER-REPORTING AND REPORTING DELAY FOR MELANOMA INCIDENCE IN NEW JERSEY

ABSTRACT

There is a basic uncertainty surrounding the accuracy of melanoma incidence and trends because of delay in reporting and underreporting of melanoma cases to SEER Registries.[1-3] Studies in several states have assessed reporting delay and reporting error in order to improve case ascertainment and to allow better estimation of incidence rates.[4-10] The New Jersey State Cancer Registry (NJSCR) has yet to perform this assessment and it is unknown whether reporting problems exist. We (1) surveyed dermatologists to characterize the process by which melanoma is diagnosed and reported in New Jersey and to identify reasons why melanoma may be underestimated; (2) quantified the extent of reporting delay in New Jersey; and, (3) estimated the number of potentially missing melanoma cases using a capture-recapture analysis. Using log-linear models we found that approximately 817 melanoma cases were missing each year and that the likely source was inadequate reporting by physicians and pathology labs. Survey results showed that only 166 of the 282 (58.9%) dermatologists who were surveyed reported having a mechanism in place for reporting cases to the NJSCR. Dermatologists used 62 different outside pathology laboratories and 42 % were not reporting (31% out-of-state labs, 11% NJ labs), further contributing to the missing cases. There were 1259 melanomas (10.1%) diagnosed between 1995 and 2003 that were reported after the two year standard reporting delay and were considered late.

Hospitals and physicians were more likely to report their cases within the standard reporting timeframe. However, hospitals contributed 677 cases (53.8 %) to the cases that are reported late, indicating that these melanoma cases were not reported by the primary diagnosing source. These estimates can be used in the future to develop a method for formally adjusting for biases in cancer incidence rates and trends, ultimately improving the accuracy of melanoma incidence rates. Additionally, by determining the sources of unreported melanoma cases in New Jersey, targeted adjustments to the surveillance activities can be made to improve future completeness of melanoma case reporting.

BACKGROUND

Melanoma is widely recognized as being one of the cancers that is most affected by under-reporting and surveillance problems.[1-3] Ascertainment of melanoma cases is especially likely to be incomplete for early-stage cancers diagnosed and managed at physician offices, which unlike hospitals, do not always routinely report cancer cases to central cancer registries.[3] Melanoma is particularly susceptible to this phenomenon as the proportion of patients seen in physician offices versus hospitals for diagnosis and treatment has become increasingly more common, as socioeconomic pressures push to have more treatment shift to the outpatient setting.[1] Changes in medical practice in the 1980's[9], health care reform in the 1990's[9], and a greater awareness of melanoma prevention, has also influenced the trend toward diagnosis and treatment in non-hospital settings.[6,7]

Over the past two decades, central cancer registries have demonstrated that the under-enumeration of melanoma cases has become increasingly problematic. The underreporting of melanoma cases rose from three percent in the early 1970's to nearly 20 percent in the mid-1980's.[4,6] Studies done in Massachusetts[7], Connecticut[5], Iowa[9], and California[8], have investigated the severity of melanoma underreporting by surveying physicians, pathologists, or dermatopathologists and suggest that between 12 percent and 40 percent of melanoma cases were not being captured. These studies showed various causes of underreporting, including diagnosis or treatment (or both) in the private offices of physicians, diagnosis in out-of-state pathology laboratories, and diagnosis in non-hospital laboratories. Table 2-1 describes the studies that have been done to assess melanoma underestimation.

In New Jersey, melanoma cases are routinely collected by the New Jersey State Cancer Registry (NJSCR), a population-based cancer incidence registry that serves the entire state of New Jersey, which has a current estimated population of 8.6 million people and an average of 47,000 new cancer cases reported each year. The NJSCR was established by legislation (NJSA 26:2-104 et. seq.) in 1978 and meets the high-quality standards of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program, the Centers for Disease Control's National Program of Cancer Registries (NPCR), and the North American Association of Central Cancer Registries (NAACCR). Melanoma cases are identified from hospitals, pathology laboratories, radiation and

surgical centers, and dermatology offices. Melanoma case reports are submitted to the NJSCR within three months of hospital discharge or six months of diagnosis, whichever is sooner. In addition, reporting agreements are maintained with New York, Pennsylvania, Connecticut, Delaware, Florida, Maryland, and North Carolina so that New Jersey residents diagnosed with cancer outside the state can be identified. Out-of-state reports are uploaded to the New Jersey State Cancer Registry annually. Therefore, there is a standard delay time of two years between cancer diagnosis and the first report of cancer incidence data to the public. However, case reporting is fluid and newly discovered or erroneous cases are constantly being added or deleted in the existing data file. When the new data is released each year, the previous years of data are also updated, as is consistent with other cancer registries.[8]

Incidence rates can be underestimated if there is a delay in case reporting and reporting error can cause incidence rates to be overestimated if cases are reported incorrectly. Clegg et al., found that that a significant delay in the reporting of melanoma cases resulted in the appearance of a decline in melanoma incidence among white males. After adjusting for the delay in reporting, this study demonstrated that it is evident that melanoma incidence continues to increase rapidly.[2] Therefore, it is evident that under- and late- reporting can result in errors in incidence and trends, which has important implications for public health surveillance and policy.

Current data from the New Jersey State Cancer Registry (NJSCR) demonstrate that melanoma incidence is increasing at a faster rate in New Jersey than nationally, growing by 4.7 percent between 2003 and 2007 which was the second largest statistically significant increase in site-specific incidence during those years.[11] New Jersey ranked in the top third of all U.S. states for melanoma incidence in 2008 and has increased annually from 11.2 per 100,000 in 1990 to 21.4 per 100,000 in 2008 (the most complete year of data available from NJSCR). Although these data clearly demonstrate the necessity of melanoma prevention and early detection, evidence from other central cancer registries suggest that New Jersey melanoma incidence rates may be underestimated.

Several other cancer registries have demonstrated that the under-enumeration of melanoma cases has become increasingly problematic (Table 2-1). In New Jersey such an assessment has not been completed. This study proposes to (1) survey dermatologists to characterize the process by which melanoma is diagnosed and reported in New Jersey and to identify reasons why melanoma may be underestimated; (2) quantify the extent of reporting delay in New Jersey; and, (3) to estimate the number of potentially missing melanoma cases using a capture-recapture analysis. By conducting a thorough assessment of melanoma reporting we can depict the impact of these problems on melanoma incidence data for New Jersey.

METHODS

The assessment of under- and late- reporting for melanoma in New Jersey occurred in three parts, as described in the following subsections. All data analyses were generated using SAS software, Version 9.2 for Windows © 2002-2008 SAS Institute Inc., Cary, NC. Tables and figures were created using Microsoft Excel version 2010.

PART ONE: SURVEY OF DERMATOLOGISTS

A survey of New Jersey dermatologists was developed to identify the process by which dermatologists were reporting melanoma cases; to estimate the number of melanoma cases handled by each physician / group practice each year; and, to identify pathology laboratories that were used for dermatology specimens that have not been reporting to the NJSCR. We delineated current reporting practices for melanoma in this manner so that we could identify possible reasons that cases may be missed.

The survey was designed to be a non-threatening, information gathering tool rather than an enforcement tool by the NJSCR as a regulatory body. The survey tool was a combination of questions used in the survey conducted by the San Francisco/Greater Bay Registry in 2006[8] and questions that have been used previously by the NJSCR. The survey included 15 items to gather information about the number and location of offices in which the physician practices, whether surgery is performed in the office(s), the

outside pathology laboratories used for interpretation, percentage of specimens that are interpreted personally, the mechanisms in place for reporting cases to the NJSCR, any barriers to reporting, and if the physician was interested in electronic reporting. The questions that we utilized to estimate the numbers of melanoma cases for each office were:

- How many cases of invasive cutaneous melanoma have you seen in the past year?
- How many cases of invasive cutaneous melanoma have you seen in the past five years?
- How many cases of *in situ* cutaneous melanoma have you seen in the past year?
- How many cases of *in situ* cutaneous melanoma have you seen in the past five years?

A master directory of dermatologists and dermatopathologists practicing in New Jersey was compiled using listings from the Dermatological Society of New Jersey, the American Academy of Dermatology, National Provider Index (NPI), Yellow Pages listings for New Jersey dermatologists, and internet searches of "New Jersey dermatologists" and "dermatopathologists" using physician search engines (e.g., healthgrades.com). Additionally, the NJSCR was used to identify physicians who have reported melanoma cases in the past, although this method was limited because individual physician names have not been recorded consistently. Quality control measures were utilized to assure

that the resulting list uniquely identified each physician. The survey was mailed to dermatologists or their practice managers, along with an information sheet with frequently asked questions (FAQ's) for melanoma reporting. Physicians were given the opportunity to return the completed survey by mail using an enclosed postage-paid envelope or by fax. If the physician did not return the survey after two months, a second survey was mailed. To encourage participation, we phoned five percent of the dermatologist offices to follow-up and ask if there were any questions about the survey. At that time, the dermatologist/practice manager had the option to complete the questions over the phone. A third, 'short' version of the survey, which included a checklist of commonly used pathology laboratories, was mailed to the remaining dermatologists who had not returned the survey after five months.

Statistical Analysis for Survey

Frequency distributions were calculated for survey items. Average annual estimates of melanoma cases were calculated using the number of cases seen in the past five years. If the physician did not provide a five year estimate or was not in practice for five years, we used the physician's estimate for the number of cases seen in one year. Pathology laboratories that were listed by dermatologists as processing dermatology specimens were cross-referenced with the pathology laboratories known to be reporting to the NJSCR.

PART TWO: REPORTING DELAY

To quantify the effects of reporting delay, we created two-dimensional triangular tables of initial melanoma incidence case counts reported at the 2-year standard delay time and the addition of cases identified at subsequent data submissions, using methods similar to Clegg et al.[2] Data were extracted from the NJSCR for individuals who were diagnosed with invasive and *in situ* melanoma of the skin (ICD-O-3 site C440-C449, ICD-O-3 histology type 8720-8790.) for the diagnosis years 1995 through 2009. Report dates were analyzed by number of years after diagnosis.

In order to characterize the sources of delayed reporting, a dataset of melanoma cases was created using the New Jersey State Cancer Registry (ICD-O-3 site C440-C449; histology type 8720-8790, invasive behavior). Diagnosis years were restricted to the years 1995 through 2003 and we retained reporting information (reporting source, reporting date) for diagnosis year plus five years to examine reporting intervals. Possible reporting sources were: physicians and physician groups (Physicians), New Jersey hospitals and ambulatory care centers (NJ Hospitals), out-of-State hospitals (OoS Hospitals), death certificates (DC), and independent laboratories (labs). To calculate the time interval between diagnosis and reporting, we subtracted the diagnosis date from the date first reported to the NJSCR. Time intervals were calculated as years and rounded to the closest whole number. Cases were considered "late" if the interval between diagnosis and first report was greater than two years, the standard delay time.

Part Three: Capture – Recapture Estimation

To estimate the total population of melanoma cases and the approximate number of missing melanoma cases, a three source capture-recapture analysis was used. Capture-recapture methods use a series of two or more data sources to estimate the true population size based on the number of cases captured jointly and independently by each of the data sources.

Data Sources

Cases reported by New Jersey hospitals and ambulatory care centers to the NJSCR were used as the first source of data for the capture-recapture analysis. New Jersey regulations (NJAC 8:57A) require the reporting of all newly diagnosed cancer cases to the NJSCR within three months of hospital discharge or six months of diagnosis, whichever is sooner; and follow-up reports shall be submitted on each cancer case at least annually to confirm the patient's vital status. Legislation also requires that hospitals report cases electronically. Physicians and physician groups were the second source of melanoma cases. A physician is required to report electronically if s/he sees more than 100 cases per year; however, most of the melanoma cases reported to the NJSCR by physicians are paper-based reports that are sent via mail. The electronic reports from independent pathology laboratories (E-path) database were the third data source that was used for the capture-recapture analysis. Epath is an automated electronic process for accessing and using pathology reports to identify cancer cases.

The information collected and included in the pathology laboratory reports represents a critical data source for state cancer registries. Melanoma cases from the three sources were matched based on name, birthdate, address, social security number (if available), data of diagnosis, primary site, and histology.

The three sources were considered fairly complete because active surveillance in the form of auditing is performed on New Jersey hospitals, hospital owned/operated radiation facilities and independent laboratories. The NJSCR also performs follow back procedures for cases that are identified by independent laboratories and 'Follow-Back Physician Reporting Forms' are mailed to the requesting physician for treatment information.

Data were entered into a 2^3 contingency table, where 3 is the number of sources. Table 2-4 shows the pairwise matching of the three sources to represent the full recapture history of the melanoma cases, where n_{123} denotes the number of cases captured in data source 1, source 2, and source 3. The value n_{12} denotes the number of cases captured in data source 1 and source 2, but is absent in source 3, and so on. The cell containing "n?" represents the number of cases not reported by any of the sources and is the main interest in this analysis.

We used the 3-source capture-recapture model to estimate the total number of melanoma cases.[12] Specifically, we fitted a series of log-linear models including interactions between at least two of the three sources that take into account the possible dependence structure between sources or heterogeneity of capture.[12] Chi-square statistics were used to identify statistically significant dependencies between pairs of sources. The choice of the final model was based on Akaike Information Criterion (AIC).[13] The total number of melanoma cases and the number of missing cases were estimated from the final model. Their respective 95 percent confidence intervals (95% CI) were also provided.

RESULTS

PART ONE: SURVEY OF DERMATOLOGISTS

We identified and sent a survey to 422 New Jersey dermatologists and dermatopathologists, covering over 60 group practices. Eleven physicians were excluded because we could not locate him/her (n=9) or because s/he was deceased (n=2). Of the remaining 411 physicians, 81 percent responded (n=332) and it was determined that 282 were eligible (282/332; 85%). Fifty physicians were ineligible for analysis because s/he had relocated to another state (n=20), had retired (n=18), or reported not diagnosing melanoma (n=12). Most dermatologists reported working in one main office; approximately 20 percent had two offices and fewer than 3 percent

had more than two offices. Over 95 percent reported that they do not interpret the melanoma biopsy specimens and that the specimens were sent to external pathology laboratories for diagnosis. The number of physicians performing surgery for cutaneous melanoma were divided fairly evenly – 32.5 percent did not perform surgery, 27.7 percent performed surgery on *in-situ* only, and 39.7 percent performed surgery for invasive and *in-situ* melanoma.

Only 166 of the 282 (58.9%) dermatologists who were surveyed reported having a mechanism in place for reporting cases to the NJSCR. The majority (112/166; 68%) of the cases were reported on paper forms via mail, which contributes to the reporting delay. Several of the responding dermatologists acknowledged that they were unaware of their reporting responsibilities – over 15 percent thought the responsibility of reporting was being covered by the hospital, lab, or other facility. Ten percent of the respondents specifically stated that "the pathology laboratory should be responsible for reporting melanoma cases." This lack of awareness can result in the under-reporting of melanoma cases. Other reasons that were listed as barriers to reporting to the NJSCR were: lack of resources/staff (34.7%), lack of time (43.3%), no good mechanism in place (22.7%), or question the utility of reporting (5%).

Survey results showed that dermatologists used 62 unique pathology laboratories and only 24 (38.1%) were based in New Jersey. There were seven (11%) newly identified

pathology labs in New Jersey that were not currently reporting cases to the NJSCR. A majority (61.9%) of the pathology labs identified were out-of-state, only half of which were actively reporting melanoma cases to the NJSCR. There were 62 (22%) physicians who were using non-reporting pathology labs for dermatology specimens. Using the estimates provided by this group of dermatologists, we calculated that there were possibly over 170 invasive cutaneous melanomas per year not being reported by labs. A total of 26 dermatologists (9.2%) did not have a mechanism in place for reporting melanoma cases to the NJSCR and were also using labs that did not report to the NJSCR. We estimate conservatively that this combination explains at least 50 missing melanoma cases per year, using the approximations provided by the respective dermatologists.

The 244 responding dermatologists (comprising 67.6 percent of the identified practicing dermatologists in New Jersey) saw an estimated 1104 melanomas each year based on the self-reported numbers. Nine physicians who declined to provide melanoma estimates and 28 who reported that they only saw *in-situ* melanoma cases were not included in the relevant calculations.

Part Two: Reporting Delay

Two years after diagnosis, there were 1,194 cases of malignant melanoma of the skin for individuals diagnosed in 1995. In 1998 there were 75 more cases reported, and, in 1999

there were 54 more cases reported. See Table 2-2 for the complete depiction of reporting delay for incident melanoma cases in New Jersey residents. A majority of the cases were accrued within seven years after diagnosis, but cases continued to be accrued for 16 years after diagnosis. The count of individuals diagnosed with melanoma in the year 1995 reached 1416 in 2011. Similar reporting patterns were seen for each year of diagnosis.

There were 1259 melanomas (10.1%) diagnosed between 1995 and 2003 that were reported after the two year standard reporting delay and considered late. In Table 2-3 the reporting intervals are shown by reporting source. Cases reported from death certificates and out-of-state facilities were more likely to be reported late (2-5 years) compared to cases reported from independent pathology laboratories, New Jersey hospitals, and physicians. Of the cases reported by New Jersey hospitals, 64.7 percent were reported within a year of diagnosis and of the cases reported by physicians, 77.2 percent were reported within one year of diagnosis. When examining the distribution of reporting sources for the cases considered late, we calculated that that hospitals contributed 677 cases (53.8 %), out-of-state facilities reported 444 (35.3 %), physicians reported 78 (6.2%), independent pathology laboratories contributed 41 (3.3%), and 19 came from death certificates (1.5%).

PART THREE: CAPTURE – RECAPTURE ESTIMATION

For this analysis, 1708 melanoma cases were identified in the NJSCR as being diagnosed in 2008 by the three different sources – ambulatory care/hospitals (n=1392), physician/group practices (n=650), and independent pathology laboratories (n=245). Table 2-4 shows the data schema for the capture-recapture analysis.

Figure 2-1 presents the cross-matches from each source. There were eight different combinations of the three sources identified. The number of unique cancer cases identified by each combination of sources is presented in Table 2-5. The majority of the cases (58%) were reported solely from Hospitals/Ambulatory Care Centers. The Physician – Lab combination, the expected reporting combination for early stage melanoma cases, comprised 7.2 percent of the reported cases.

The count data from Table 2-5 served as the input for the capture-recapture model. All main effects were significant ($p<0.0001$). Chi-square analyses were used to test for dependencies between pairs of sources and the interaction terms between Hospital and Lab, Hospital and Physician, and Physician and Lab. All demonstrated a statistically significant dependency ($p<0.0001$). We estimated the total population by fitting log-linear models for the two and three source interactions, with results summarized in Table 2-6.

The log-linear model chosen was the model that included the main factors and the interaction term between physicians and pathology laboratories, which had the lowest AIC and also had strong empirical content (physicians are providing specimens to the pathology laboratories for diagnosis.) The final model estimated 2525 total cases (95% CI = 2251.8 – 2840.0) and predicted that 817 (95% CI = 692.2 – 960.4) melanoma cases are being missed by all three sources. Observed values from physicians and independent labs were underestimated compared to the observed values for the hospital categories. Table 2-7 provides observed and estimated values for the fitted model.

DISCUSSION

Despite the number of surveillance activities conducted by the NJSCR, we have found that melanoma cases remain unreported in New Jersey each year, as other central cancer registries have also demonstrated. Koh et al. found that this underestimation of melanoma incidence is a problem for nearly all cancer registries nationwide.[14] We experienced similar melanoma reporting patterns in New Jersey as demonstrated in other registries –missing cases occurred when non-reporting physicians performed office-based biopsies, used non-hospital based dermatopathology labs, and/or used out-of-state labs.

Using the model from the capture-recapture analysis we were able to compare three sources of melanoma cases and critically evaluate the number of missing cases. We approximated that an additional 817 cases were considered missing each year and that the likely source of the missing cases was inadequate reporting by physicians and pathology labs.

Results from the survey of dermatologists showed that there was a lack of awareness of reporting responsibilities among dermatologists, which may have contributed to the reason why physicians did not report melanoma cases to the NJSCR. The dermatologists who completed the survey estimated that they saw approximately 1107 melanoma cases each year, representing melanoma cases seen by 67.6 percent of the identified New Jersey dermatologists. Twelve dermatologists (4.3%) specifically stated that they were "unaware of [reporting] policy" or "did not know that it was required." Physicians who were not performing surgery were relying on the hospitals and pathology laboratories to report the cases. More frequently, physicians assumed that "the laboratory making the diagnosis did the reporting" or that the pathology labs should be the main source for reporting melanoma cases to the NJSCR. Similarly, Cockburn et al. found that many dermatologists in California were unaware that they were required to report the melanoma, or they assumed that the laboratory of the hospital would report the case.[8] If a physician diagnoses, performs the surgical removal in the office,

evaluates his/her own slides, and does not report the case to the NJSCR - the case is being missed.

Likewise, when a dermatologist sends specimens to a laboratory outside of New Jersey for processing, there is a risk of missing the case completely if the physician does not report the case because the NJSCR does not have the authority to mandate reporting from out-of-state laboratories. Often these labs report back to the doctor only. We found that a majority of the labs being used for dermatology specimens were out-of-state facilities, and likely a main source of the delayed cases in New Jersey. There were also labs that were only reporting cases to the state in which they were located causing missed cases if the physician never reported. For instance, a lab in New York was only reporting New York residents diagnosed with cancer to the state registry, rather than all cancer cases to the state registry. To compound the problem, we estimated that nearly 10% of the dermatologists using non-reporting labs were non-reporters themselves.

Reporting delay was also evident. As expected, hospitals are principally responsible for the melanoma cases that are submitted in a timely manner and cases reported from death certificates and out-of-state facilities are coming in later. Although 77.2 percent of cases reported by physicians were also reported within a year of diagnosis, there were many cases reported late by hospitals (n=677) indicating that incomplete reporting may be occurring when a physician does not report a case to the registry upon diagnosis

and the case is reported by a hospital at a later date. For melanoma cases, this typically occurs when a previously diagnosed patient is admitted to the hospital for a wide re-excision of a previous biopsy or surgery; or a hospital radiation/oncology department administers treatment. Another example is when a melanoma case is reported only by the pathology laboratory and not the diagnosing physician. The NJSCR staff must "follow-back" to the hospital/physician to obtain further information about the diagnosis.

There are several nuances to cancer reporting in New Jersey, which may affect melanoma reporting adversely. First, small pathology laboratories that cater to specialties (e.g., dermatology and urology) have become more prevalent. These "boutique labs" offer customized services that are more attractive than the less-personalized, large, nationwide pathology laboratories that may be more expensive also. Although "boutique labs" tend to be local, the challenge arises when trying to actively identify the new labs in a timely manner. Labs that are not known to the NJSCR and are not reporting comprise 11 percent of the labs diagnosing dermatology specimens in New Jersey. Depending on how long it takes for identification, cases that are eventually reported by the lab would be late – adding to reporting delay.

A second complexity is that New Jersey is particularly susceptible to delays in reporting because of its geographical location. Many New Jersey residents seek out-of-state

medical care because of the close proximity to cancer centers in major metropolitan areas. Approximately 7,500 case reports (all cancers combined) are received annually through reciprocal reporting agreements with other states, contributing to approximately 6% of the total caseload. New Jersey residents who are diagnosed and/or treated in hospitals in the surrounding states are reported, albeit with some delay, to the NJSCR under this reciprocal reporting arrangement. For New Jersey residents who were diagnosed with melanoma in between 2004 and 2008, approximately 17 percent were diagnosed, treated and reported solely by an out-of-state facility (from unpublished work by the NJSCR). This is the result of several large dermatology group practices and dermatology "boutique labs" in New York City and Philadelphia. Although cases from these facilities were eventually reported, the nature of reciprocal reporting adds to reporting delay. The reporting delays that occurred from the "boutique labs" and the out-of-state labs reinforce the importance of timely reporting by the physician.

The main limitation in this study was incompleteness of data. Some dermatologists who were known to handle a large proportion of melanoma cases did not return our survey. Although we do not know all of the reasons that dermatologists did not return the survey, six returned a blank survey with indications that they felt that they were "already fulfilling their case reporting obligations." Survey non-responders could introduce bias because they are probably less likely to report melanomas; however, this

would result in an underestimate of the true proportion of unreported melanomas. It is also possible that dermatologists may under/overestimate when they provide the number of melanomas diagnosed per year. We minimized this problem by using the annual average when possible. There is also a slight risk of recall bias if dermatologists were providing estimates based on memory rather than examining the records. We tried to reduce this risk by sending the surveys to office managers when available.

It is possible that the actual number of missing cases may be slightly lower because of the trends seen with reporting delay. At the time that the subset of cases was created only one and a half years had passed. Therefore, it is likely that cases being reported for the diagnosis year 2008 were not as complete as possible.

In addition to providing insight on melanoma underestimates, another strength of this approach was that it facilitated the identification of New Jersey and out-of-state laboratories specializing in melanoma pathology. Additionally, this model for case finding can be adapted to other cancer sites, such as early stage prostate cancer, where a large number of cases are diagnosed and treated in an outpatient setting.

In the future, a process by which emerging laboratory operations can be identified quickly is essential. Recognition of new entities will allow for more complete melanoma

case ascertainment. In Iowa, Merlino et al.[4] found that outreach to pathology laboratories led to an increase in the proportion of cases identified by independent labs from 1.3 percent to 15.2 percent, and the subsequent decrease in the proportion of cases reported from hospitals/clinics. Similarly, researchers in California determined that there is potential for a substantial undercount of melanoma cases due to non-reporting by a majority of physicians, combined with increasing use of third party pathology facilities that are not routinely canvassed by the cancer registry, and the increasing frequency of in-house pathology in non-reporting facilities.[8] California registries were also able to make relatively small, targeted adjustments to the surveillance activities that substantially improved the completeness of melanoma registration. Lai et al.[10] found that, in an analysis of the Kansas Cancer Registry, about 40 percent of the invasive melanoma cancers diagnosed in 1999 and 2000 were reported only by dermatopathologists / physicians via pathology reports. Most of the non-reporting was due to pathology laboratories and physician non-reporting. Once they increased that reporting, they found that most cases were reported within 12 months of diagnosis. By implementing methods used at other central cancer registries, New Jersey can also benefit from improved case ascertainment.

The value and importance of melanoma surveillance must be promulgated among dermatologists and other providers by central cancer registries. Five percent of the responding physicians questioned the utility of reporting. The lack of awareness of

reporting requirements and the reliance on pathology laboratories as the primary reporting source also speaks to this issue. Perhaps as the health paradigm continues to shift to the outpatient setting for dermatology and other specialties, central cancer registries should target specialty physicians and physician assistants with education about reporting.

CONCLUSION

By determining the sources of unreported melanoma cases in New Jersey, we were able to provide specific information to guide changes for surveillance activities that can greatly improve the completeness of melanoma case reporting. Quantifying the under-reporting and reporting delay provides a useful tool for better estimation of melanoma incidence rates and trends.

TABLE 2-1: STUDIES ADDRESSING MELANOMA UNDERESTIMATION, REPORTING DELAY AND REPORTING ERROR

Study	Registry	Dates	Percent Underreported	Method
Cockburn et al., 2008[8]	Los Angeles	2005-2006	30 to 40%	Survey of dermatologists and dermatopathologists
	Greater San Francisco Bay	2006		
Lai et al., 2004[10]	KS	1995-2000	50%	Registry Analysis
Merlino et al., 1997[9]	IA	1977-1994	10 to 17%	Survey of dermatologists
Seiffert, 1992[4]	Northern California	1973-1985	4% in 1973 to 16% in 1985	Physician and pathology lab records
Bolognia et al., 1992[5]	CT	1990-1991	10 to 20%	Survey of dermatologists
Koh et al., 1992[14]	PR, CA, CO, CT, IA, MI, MO, NH, RI, TX, WY	1992	1 to 24%	Survey of cancer registries
Koh et al., 1992[7]	MA	1982-1986	12 to 19%	Survey of pathologists
Karagas, 1991[6]	WA	1974-1984	2% in 1974 to 21% in 1984	Survey of reporting physician / pathology lab

TABLE 2-2: REPORTING PATTERNS FOR INCIDENT MELANOMA CASES TO THE NJSCR FOR 1995-2009 DIAGNOSIS YEARS

Year Submission	Year of Diagnosis														
	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
1997	1194														
1998	75 (6.3)	1539													
1999	54(4.5)	66 (4.3)	1868												
2000	32 (2.7)	43 (2.8)	103 (5.5)	1912											
2001	24 (2.0)	18 (1.2)	41 (2.2)	34 (1.8)	2069										
2002	16 (1.3)	13 (0.8)	22 (1.2)	20 (1.0)	51(2.5)	2271									
2003	3 (0.3)	8 (0.5)	10 (0.5)	10 (0.5)	8 (0.4)	30 (1.3)	2700								
2004	6 (0.5)	6 (0.4)	2 (0.1)	14 (0.7)	9 (0.4)	13 (0.6)	83 (3.1)	3343							
2005	4 (0.3)	2 (0.1)	4 (0.2)	9 (0.5)	6 (0.3)	11 (0.5)	38 (1.4)	40 (1.2)	2945						
2006	3 (0.3)	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)	12 (0.5)	6 (0.2)	16 (0.5)	23 (0.8)	3204					
2007	1 (0.1)	2 (0.1)	3 (0.2)	1 (0.1)	5 (0.2)	5 (0.2)	7 (0.3)	7 (0.2)	10 (0.3)	24 (0.7)	3241				
2008	1 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	3 (0.1)	6 (0.3)	10 (0.4)	3 (0.1)	3 (0.1)	11 (0.3)	36 (1.1)	3496			
2009	0 (0.0)	0 (0.0)	6 (0.3)	3 (0.2)	1 (0.0)	3 (0.1)	2 (0.1)	2 (0.1)	3 (0.1)	7 (0.2)	3 (0.1)	45 (1.3)	3760		
2010	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.1)	3 (0.1)	3 (0.1)	2 (0.1)	2 (0.1)	3 (0.1)	5 (0.2)	10 (0.3)	35 (0.9)	3553	
2011	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.1)	3 (0.1)	0 (0.0)	1 (0.0)	2 (0.1)	9 (0.3)	2 (0.1)	9 (0.2)	28 (0.8)	3616
Total in 2011	1416	1701	2062	2007	2158	2356	2852	3413	2987	3251	3294	3553	3804	3581	3616

The first number in each column is the number of cases received within two years after the diagnosis year. The following cells contain the number of cases and percentage increased by year after the first two years after diagnosis. For instance, in 1995 there were 1194 cases of melanoma reported to the NJSCR by 1997. However, an additional 75 cases were reported in 1998 and 54 more in 1999, and so on. Cases diagnosed in 1995 continued to be reported for 10 years after diagnosis.

Note: Melanoma in situ and invasive cases were included.

TABLE 2-3 : REPORTING DELAY FOR MELANOMA CASES DIAGNOSED BETWEEN 1995 AND 2003 AND FOLLOWED FOR FIVE YEARS* BY FIRST REPORTING SOURCE (N=12,516)

First Reporting Source	Time Between Diagnosis and Report					
	<1 year		1-2 years		2.1 - 5 years**	
DC	0	0.0%	8	29.6%	19	70.4%
LAB	738	53.1%	610	43.9%	41	3.0%
NJH	4961	64.7%	2033	26.5%	677	8.8%
OOS	364	22.2%	828	50.6%	444	27.1%
PHY	1384	77.2%	331	18.5%	78	4.4%

* For each year of diagnosis, only five years of follow-up data are included for analysis purposes. More data is available through the NJSCR.

**Two years = standard delay time. Cases reported after two years are considered late/delayed.

DC = Death Certificate; LAB= independent pathology laboratory, NJH= NJ hospital or ambulatory care center; OOS= Out-of-State hospital or other facility; PHY= physician or physician group practice

TABLE 2-4: THREE-SOURCE CAPTURE-RECAPTURE SCHEMA

		Source 1 : Hospitals & Amb Care Ctrs			
		Present		Absent	
		Source 2: Physicians			
		Present	Absent	Present	Absent
Source 3:	Present	n_{123}	n_{13}	n_{23}	n_3
Independent Labs	Absent	n_{12}	n_1	n_2	n?

TABLE 2-5: UNIQUE COMBINATIONS OF SOURCES IDENTIFYING MELANOMA CASES IN 2008

	Source 1	Source 2	Source 3		
	Hospital / Ambulatory Care Sources	Physician / Group Practice	Independent Pathology Laboratory	Count	Percent
n_1	Yes	No	No	1004	(58.8%)
n_{12}	Yes	Yes	No	273	(16.0%)
n_{13}	Yes	No	Yes	47	(2.7%)
n_{123}	Yes	Yes	Yes	68	(4.0%)
n_2	No	Yes	No	186	(10.9%)
n_{23}	No	Yes	Yes	123	(7.2%)
n_3	No	No	Yes	7	(0.4%)
n?	No	No	No	?	

Data used are from the New Jersey State Cancer Registry RM analytic file that was created on 30 October 2009; all cases were diagnosed with invasive melanoma in 2008.

TABLE 2-6: TOTAL NUMBER OF MELANOMA CASES BASED ON LOG-LINEAR MODELS OF MULTIPLE REPORTING SOURCES IN NEW JERSEY, 2008

Interaction term used in the model	df	AIC	Estimate of total cases	95% CI
None	3	421.0	2257	2035.2 - 2506.8
Hospitals-Physicians	2	292.5	1751	1578.9 - 1968.1
Hospitals-Labs	2	391.9	2132	1906.0 - 2391.1
Physicians-Labs	2	114.0	2525	2251.8 - 2840.0
Hospitals-Physicians-Labs	2	404.7	2338	2088.2 - 2625.2

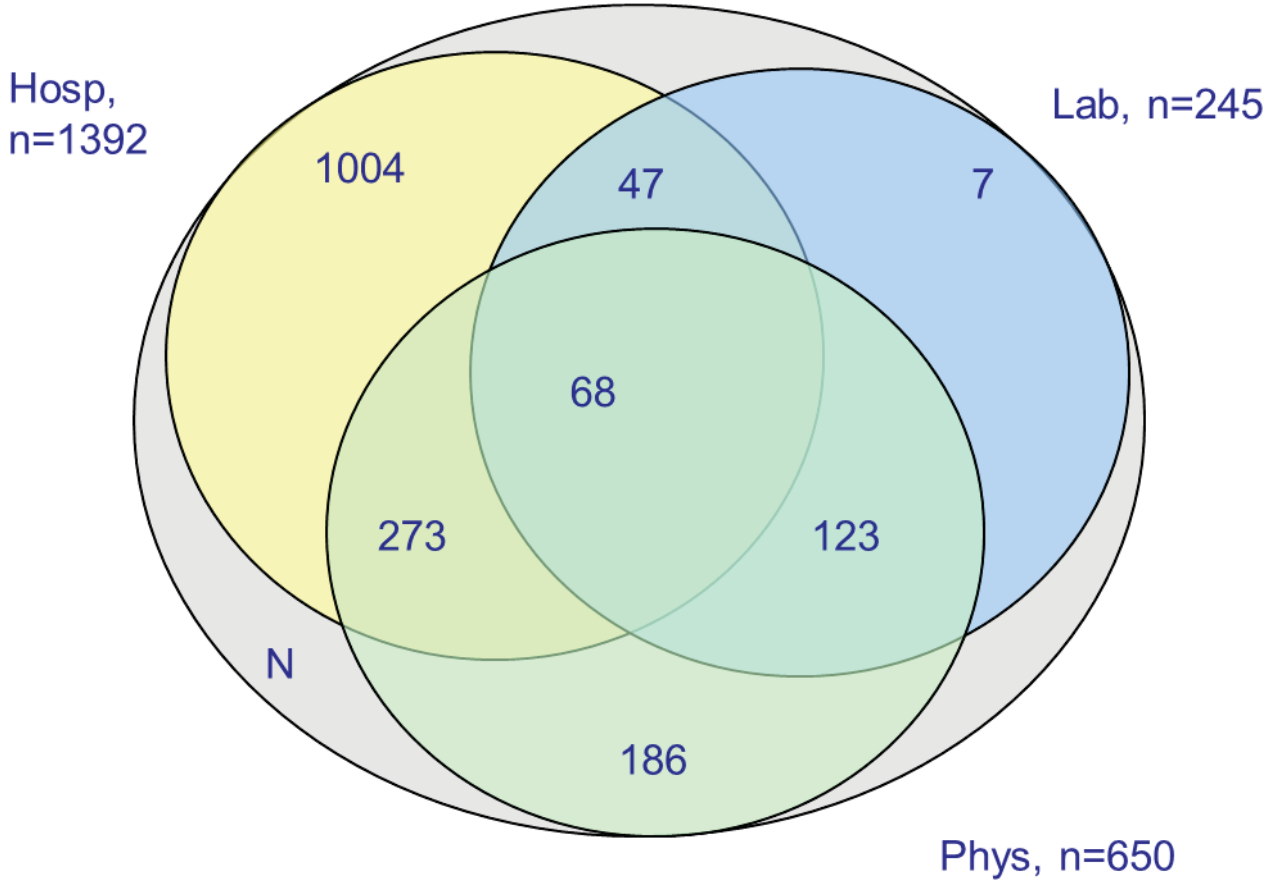
AIC, Akaike Information Criterion; CI, Confidence Interval

TABLE 2-7: PREDICTED VALUES OF MELANOMA CASES BY REPORTING SOURCE USING THE PREFERRED* LOG-LINEAR FITTED MODEL

Observed Value	Reporting Sources			Predicted Value	95% CI		
	H	P	L				
.	0	0	0	817.7	696.2	-	960.4
7	0	0	1	24.2	18.3	-	32.0
186	0	1	0	206.0	182.2	-	232.9
123	0	1	1	85.7	72.8	-	101.0
1004	1	0	0	1004.0	943.8	-	1068.1
47	1	0	1	29.8	22.6	-	39.2
273	1	1	0	253.0	225.9	-	283.3
68	1	1	1	105.3	90.0	-	123.1

CI, Confidence Interval; H, hospitals and ambulatory care centers;
P, physicians and physician groups; L, independent pathology laboratories
* The preferred model uses the physician-laboratory interaction term.

FIGURE 2-1: PRIMARY SOURCES OF MELANOMA CASES SUBMITTED THE NJSCR FOR THE 2008 DIAGNOSIS YEAR – CROSS MATCHES BETWEEN THREE SOURCES



REFERENCES

(1) Rigel DS, Friedman RJ, Kopf AW. The incidence of malignant melanoma in the United States: issues as we approach the 21st century. Journal of the American Academy of Dermatology 1996; 34(5 Pt 1):839-847.

(2) Clegg LX, Feuer EJ, Midthune DN, Fay MP, Hankey BF. Impact of reporting delay and reporting error on cancer incidence rates and trends. Journal of the National Cancer Institute 2002; 94(20):1537-1545.

(3) Hall HI, Jamison P, Fulton JP, Clutter G, Roffers SD, Parrish P. The Reporting of Cuteneous Melanoma to Cancer Registries in the United States. Journal of the American Academy of Dermatology 2003; 49: 624-630.

(4) Seiffert J. Statbite: Underreporting of melanoma. Journal of the National Cancer Institute 1992; 84(5): 289.

(5) Bolognia JL, Headley A, Fine J, Berwick M. Histologic evaluation of pigmented lesions in Connecticut and its influence on the reporting of melanoma. Journal of the American Academy of Dermatology 1992; 1992 Feb;26(2 Pt 1):198-202.

(6) Karagas MR, Thomas DB, Roth GJ, Johnson LK, Weiss NS. The effects of changes in health care delivery on the reported incidence of cutaneous melanoma in western Washington State. American Journal of Epidemiology 1991; 133(1):58-62.

(7) Koh HK, Clapp RW, Barnett JM, Nannery WM, Tahan SR, Geller AC et al. Systematic underreporting of cutaneous malignant melanoma in Massachusetts. Possible implications for national incidence figures. Journal of the American Academy of Dermatology 1991; 24(4):545-550.

(8) Cockburn M, Swetter SM, Peng D, Keegan TH, Deapen D, Clarke CA. Melanoma underreporting: why does it happen, how big is the problem, and how do we fix it? Journal of the American Academy of Dermatology 2008; 59(6):1081-1085.

(9) Merlino LA, Sullivan KJ, Whitaker DC, Lynch CF. The independent pathology laboratory as a reporting source for cutaneous melanoma incidence in Iowa, 1977-1994. Journal of the American Academy of Dermatology 1997; 37(4):578-585.

(10) Lai SM, Garimella S, Keighley J. Pathology and dermatology reports: Key in completeness of melanoma cancer reporting in population-based cancer registries. Journal of Registry Management 2004; 31(3): 87-91.

(11) Cancer in North America, 2003-2007. Volume One: Combined Cancer Incidence for the United States and Canada. Springfield, IL: North American Association of Central Cancer Registries, 2010.

(12) McClish D, Penberthy L. Using Medicare Data to Estimate the Number of Cases Missed by a Cancer Registry: A 3-source Capture-Recapture Model. Medical Care 2004; 42(11): 1111-1116.

(13) Hook EB, Regal RR. Capture-recapture methods in epidemiology: methods and limitations. [Erratum appears in Am J Epidemiol 1998 Dec 15;148(12):1219]. Epidemiologic Reviews 1995; 17(2):243-264.

(14) Koh HK, Geller A, Miller DR, Clapp RW, Lew RA. Underreporting of cutaneous melanoma in cancer registries nationwide. Journal of the American Academy of Dermatology 1992; 27(6 Pt 1):1035-1036.

CHAPTER 3 SKIN SELF-EXAMINATION AND LONG-TERM MELANOMA SURVIVAL

ABSTRACT

BACKGROUND: While melanoma is highly curable if detected in its earliest stages and treated properly, the survival rate for late stage disease is poor. Skin self-examination (SSE) is a useful and inexpensive screening method that has the potential to reduce the risk of advanced disease. Since melanoma commonly recurs as late as 10 years after diagnosis, the purpose of this study is to estimate long term survival rates for individuals diagnosed with melanoma who performed SSE versus those who did not in the presence of competing risks. METHODS: Subjects were drawn from a previously conducted case-control study of Connecticut residents who were newly diagnosed with cutaneous malignant melanoma between January 15, 1987 and May 15, 1989 and followed through 2007. A competing risks analysis was conducted using death from melanoma as the failure of interest and other causes of death as competing risks. Cumulative incidence functions were calculated and compared between subjects who performed SSE (yes/no) using Gray's test. Proportional subdistribution hazards regression models were fitted using methods proposed by Fine and Gray.[1] RESULTS: Forty-five percent of cases were deceased at the end of follow-up and 48.4% were melanoma-related deaths. The cumulative incidence curves for SSE and no SSE were not statistically different (p=0.32) for death due to melanoma in the presence of competing risks. Univariate analyses suggested a 75 percent lower risk of melanoma death for those who

performed SSE compared to those who did not perform SSE (HR = 0.75, 95% CI = 0.43-1.32, p = 0.32); however when regression coefficients were adjusted for covariates using the competing risks multivariate model, we found that risk of melanoma death increased for individuals performing SSE (HR = 1.18; 95% CI = 0.64 – 2.16, p = 0.60). Skin awareness (HR = 0.49; 95% CI = 0.31 – 0.77, p = 0.002) was independently associated with decreased risk of melanoma death while increasing Breslow Depth was significantly associated with increased risk of melanoma death in the presence of competing risks (HR = 1.21, 95% CI = 1.13 – 1.29, p < 0.001). CONCLUSIONS: Although we could not find a significant association between melanoma mortality and SSE, we have confirmed previous findings of the benefit of skin awareness.

BACKGROUND

The incidence of melanoma continues to increase nearly three percent per year, making melanoma the fifth leading site for cancer incidence in U.S. men and the sixth leading site for cancer incidence in U.S. women.[2] Cutaneous melanoma accounts for three-fourths of the deaths from skin cancer[3] and, in 2012, it is estimated that 9,180 people will die from melanoma. The death rate for melanoma has been decreasing in whites younger than age 50 by 3.0 percent per year since 1991 for men and by 2.2 percent per year since 1984 in women. In contrast, the death rate has been increasing by 1.1

percent per year since 1989 for men who are 50 and older and has been stable since 1990 for women who are over 50 years old.[2]

Although overall survival rates have improved, estimates are not promising for those who are diagnosed in the late stages. The five year survival rate for someone who has a melanoma tumor detected in the early stages, before the tumor has penetrated the skin, is about 98 percent. The five year survival rate falls to 63.8 percent for regional stages and 15 percent for those with advanced disease.[4,5] It is expected that 10 percent of the individuals diagnosed with melanoma will die within 10 years after diagnosis. For stage IV metastatic cutaneous melanoma, there is a median survival of 7.5 months, which is lowered to 4-6 months with metastasis to the liver. Since approximately 16 percent of melanomas are diagnosed in the late stages[2], nearly one-fifth of the people diagnosed with melanoma are given a poor chance of survival. Over time, the proportion of cases being diagnosed at later, less treatable stages has not improved. In the early 1990's 81 percent of melanoma cases were diagnosed in the early stage, which has only improved slightly to 84 percent in 2012. Over the past 23 years, the 5-year relative survival rate for distant stage melanoma has increased only from 13 percent to 15 percent survival.[2]

Melanoma is highly curable if detected in its earliest stages and treated properly. Survival is highly dependent on the thickness of the tumor at diagnosis[6] and stage[5] of

the melanoma tumor. Because most melanomas are visible on the skin surface at a curable phase in their evolution, early detection has been associated with reduced mortality from melanoma.

Skin self-examination (SSE), a careful, deliberate, purposeful examination of the skin with an optimal frequency of once every one to two months[7], is an integral aspect of secondary prevention methods worldwide because 6% to 50% of melanomas are self-detected.[8,9] The American Academy of Dermatology promotes routine SSE, which is optimally every 1-2 months.[10] Australian cancer councils recommend the practice of regular self-screening for signs of melanoma.[11] However, the United States Preventive Services Task Force found little evidence to support screening for skin cancer in the general population.[12]

SSE is an effective and easy-to-perform method for detecting melanoma in its early stages because individuals can perform the screening at home alone, or with the help of a family member. Berwick et al. determined that SSE may provide a useful and inexpensive screening method to reduce the incidence of CMM and might reduce the risk of advanced disease among melanoma patients, with the potential for a 63% reduction in mortality.[13] The results from the study demonstrate that cases who practiced SSE may reach a plateau in survival sooner than those who did not practice SSE, indicating a survival advantage. In women, the practice of routine SSE increased

the likelihood that the lesion would be self-discovered. Studies have found that between 46 and 61 percent practice routine SSE.[7,8,14-18] Weinstock et al. have tested an intervention to encourage thorough skin self-examination in a randomized trial and found it effective in increasing the performance of this procedure while resulting in only short-term increases in surgical procedures on the skin.[19] Individuals who find a suspicious lesion could then see a trained dermatologist to detect melanoma and treat the melanoma, preventing a considerable amount of mortality.

Although the disease burden is evident, and the indication that patients with thin lesions have a better prognosis, long term health outcomes of early detection have not been elucidated in the literature. The purpose of this study is to examine the relationship between SSE and long term survival in a cohort of individuals who were diagnosed with malignant melanoma.

METHODS

SUBJECTS

Subjects for this study were drawn from a previously conducted population-based case-control study of melanoma in Connecticut residents.[20] Briefly, the case population was comprised of 650 Caucasian Connecticut residents who were newly diagnosed with cutaneous malignant melanoma between January 15, 1987 and May 15, 1989. The

cases were identified through the rapid case ascertainment mechanism used by the Connecticut Tumor Registry (CTR), which was founded in 1935 and has been one of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries since 1973. All cases were pathologically confirmed.

Data Collection

Trained nurses conducted in-person interviews with all study participants, with a mean time of three months between pathologic diagnosis and interview. A structured questionnaire was used to assess basic demographics, family history of melanoma, pigmentary characteristics, health history, reproductive history, sun exposure, skin examination practices, and site of melanoma. Nurses trained in skin examination also counted nevi greater than 2 mm on the arms and backs of subjects who consented to undergo this procedure (approximately 80%). SSE was elicited by the following question: [Before your recent biopsy] did you ever (in your life) carefully examine your own skin? By this I mean actually check the surfaces of your skin deliberately and purposely? [Yes/No response]. Whether or not a person had a skin examination from a physician was determined by asking: As far as you know, did the doctor examine your skin during any of these visits [medical visits other than for a routine checkup]? [Responses: Yes / No response]

Follow-up

Cases were actively followed by biannual mail contact for five years after diagnosis, as described in detail elsewhere.[21] Individuals who did not respond were contacted by telephone. The physician on record was contacted for patients who could not be reached by telephone. Further follow-up was conducted intermittently through 2007. To ensure completeness of data for long term follow-up, several different mechanisms were employed. A record linkage was performed with the CTR to ascertain the date of death and the cause of death for individuals who were deceased. The CTR also provided the date and the source (e.g., motor vehicles record, physician record) of last contact for the individuals who were not known to be deceased. When the CTR did not have complete or current information, we attempted to obtain vital status information from the National Death Index (NDI), Social Security Death Index, and other publicly available databases and search engines. Each institution obtained annual approval from its institutional review board to carry out the study, and all subjects provided written informed consent.

Statistical Analysis

The focus of this analysis was on skin self-examination (SSE) and long term effects on melanoma survival using competing risks analysis. Specifically, the causes of failure were classified as death from melanoma and death from other causes, with the latter treated as competing risks. Individuals who were alive at the end of follow-up (1 July

2007) were censored. Follow-up time was calculated in years measured from the date of diagnosis to the date of death or censoring (whichever occurred first). Cumulative incidence functions were calculated and compared between subjects who performed SSE (yes/no) using Gray's test.[22] Proportional subdistribution hazards regression models[1] were fitted to study the effect of SSE and other covariates to determine the intermediate- to long-term melanoma survival. Covariates considered for our analysis included: stage, education, age at diagnosis, skin awareness, mitoses, Breslow depth, histology, total sun exposure, concern about mark, severe burn pain, high number of freckles, gender, ulceration, and total number of nevi. In addition to SSE, we included variables for skin examination by a physician, skin examination by a spouse or significant other, and quality of the skin examination. An index variable was created for comorbidities using methods similar to those used to create a Charlson comorbidity score[23]. An index was also created for screening behavior so that habitual screening behavior could be considered in the analysis. (Indices are described in more detail in Appendix 1.)

A series of single covariate regression analysis was performed to select clinically and statistically significant variables to use when building the final model. A relaxed significance level of alpha = 0.10 was used as a threshold to avoid incorrectly screening out variables. Regression using the backward elimination method was used to find a reduced model that best explained the data, excluding screening variables. Variables

were removed from the model based on highest p-value. When no further variables in the original model could be removed, the remaining variables formed our base model against which we compared the base model plus SSE using the Wald test. We compared the base model plus other screening variables using the Wald test. Additionally, we examined the Bayesian information criteria (BIC) [24] to avoid overfitting and to select the most parsimonious model. Sensitivity analyses were conducted to by comparing base models with similarly fitting covariates, the model with no covariates using the Wald test and method of BIC.

Descriptive statistics were performed using SAS 9.1 (SAS Institute, Cary, NC). Competing risks analysis was conducted using the R package 'cmprsk' available at www.r-project.org.

RESULTS

Nearly 45 percent of the 650 melanoma cases were deceased at the end of follow-up on 1 July 2007. The median follow-up time was 16.3 years. Of the individuals who died, 48.4 % were melanoma-related deaths. The other deaths were a result of cardiovascular disease (23.3%), primary cancers other than melanoma (13%), other health causes (13%), accidents (1.4%), and unknown causes (0.7%). Descriptive statistics (Table 3-1) were used to compare the frequency distribution of measured patient and

pathological features by SSE (Y/N). Skin self-examiners were more likely to be female (58%) and had education further than high school (70.9%).

Cumulative Incidence Estimates – Overall Survival

Risk of dying from melanoma was higher than other causes of death consecutively for 16 years, when the risk of dying from other causes surpassed melanoma deaths. The 15-year overall survival probability was 0.59 (95% CI = 0.56 - 0.63). Throughout the follow-up period, males had a statistically higher risk of dying from melanoma compared to females (p = 0.009) in the presence of competing risks (data not shown). The 15 year cumulative incidence of melanoma death for females was 0.16 (95% CI = 0.12 – 0.21) and for males was 0.25 (95% CI = 0.20 – 0.29).

Cumulative Incidence Estimates – Skin Self-Examinations (SSE)

Individuals who performed SSE at baseline had a lower incidence of death from melanoma throughout the study period, except in years two and three (Table 3-2). Risk of melanoma death continuously increased for individuals who were not performing SSE while the risk of melanoma death plateaued around ten years post-diagnosis for individuals who were performing SSE (Figure 3-1). Gray's test for equality showed that the cumulative incidence curves for SSE and no SSE were not statistically different (p = 0.32) for death due to melanoma in the presence of competing risks.

For individuals who had any type of skin exam (self, spouse/other, or physician) we also saw consistently lower estimates of the risk of dying from melanoma throughout the study period, although not statistically different (p = 0.19) from death due to melanoma in the presence of competing risks. The highest risk of dying from melanoma in the presence of competing risks was evident for people who did not have any type of skin examination and was moderately significant (p = 0.09). This effect was seen at every time point. (Table 3-3)

Competing Risks Regression

Univariate results (Table 3-4) were consistent with previous findings. Males had a statistically significantly higher risk of dying from melanoma than females in the presence of competing risks (HR = 1.58, 95% CI = 1.12-2.23, p = 0.01). Age at diagnosis and education were associated with the probability of surviving after melanoma diagnosis, with moderate statistical significance. For each one-year increase in age at diagnosis the hazard of dying increases by 1% (HR = 1.01, 95% CI= 1.00 – 1.02, p = 0.02). Individuals who had more than a high school education had a lower risk of dying (HR= 0.68, 95% CI = 0.49 – 0.95, p = 0.02). Breslow depth was strongly associated with the risk of melanoma death. For each one millimeter increase in the Breslow depth, the hazard of dying from melanoma increased by 31 percent. (HR= 1.31, 95% CI = 1.23-1.39, p < 0.0001). Presence of ulceration (HR= 2.89, 95% CI = 1.97-4.23, p < 0.001) and

presence of any mitoses (HR= 3.11, 95% CI = 2.07-4.67, $p < 0.001$) were statistically significantly related with an increased risk of death from melanoma.

All of the screening variables demonstrated an inverse relationship with the estimated risk of dying from melanoma. However, the confidence intervals included the null value. The risk of melanoma death for people who performed SSE was 75 percent lower compared to those who did not perform SSE (HR= 0.75, 95% CI = 0.43-1.32, $p = 0.32$). Compared to any type of skin exam, people who did not have skin exams had a higher estimated risk of dying from melanoma (HR= 1.34, 95% CI = 0.95-1.87, $p = 0.09$). Casual skin examiners (versus individuals who performed deliberate and purposeful SSE) also showed a decrease in the estimated risk of melanoma death (HR= 0.78, 95% CI = 0.55-1.09, $p = 0.14$). (See Table 3-4.)

Skin awareness was statistically significantly inversely associated with the risk of death from melanoma (HR= 0.49, 95% CI = 0.32-0.76, $p = 0.001$); People who had high knowledge of melanoma symptoms also had an inverse relationship with the estimated risk of dying from melanoma (HR= 0.77, 95% CI = 0.55-1.08, $p = 0.13$), although this was not statistically significant. Individuals who went to the physician because they were concerned about a particular mark on the skin had a 42 percent higher hazard of dying from melanoma (HR= 1.42, 95% CI = 1.02-1.99, $p = 0.04$). (See Table 3-4.)

Individuals who had high sun exposure for 10 years prior to diagnosis had a decreased risk of dying from melanoma (HR= 0.91, 95% CI = 0.85-0.96, p = 0.002). Likewise, as total lifetime sun exposure increased the risk of melanoma death decreased statistically significantly (HR= 0.95, 95% CI = 0.92-0.99, p = 0.006). (See Table 3-4.)

While a high number of freckles on a person was statistically significantly associated with a decrease in the risk of death from melanoma (HR= 0.54, 95% CI = 0.34-0.84, p = 0.007), individuals who had a high number of nevi, specifically large nevi, showed an increased risk for death from melanoma. Nodular melanoma had the highest statistically significant risk of death (HR = 2.19, 95% CI = 1.40 – 3.43, p < 0.0001) compared to other histology types. The estimated risk of dying increased as the weighted comorbidity score increased (HR= 1.07, CI= 0.991 – 1.16, p = 0.08), although this was not statistically significant. (See Table 3-4.)

Significant variables in the univariate analysis were entered into a multivariate competing risks regression model with death from melanoma as the outcome variable and adjusting for the effects of other relevant factors (Table 3-5). Although SSE and other screening variables were not significant in the univariate model, they were retained in the multivariate model to assess the association of SSE and long term

survival. Additionally, age and comorbidity score were forced into the model to control for confounding. After adjusting for age and/or age plus comorbidities, individuals who were performing SSE still had a decreased estimated risk of melanoma death, although these associations were not significant (HR = 0.81, 95% CI = 0.46 – 1.43, p = 0.46 and HR = 0.80, 95% CI = 0.45 – 1.41, p = 0.43, respectively). When the regression coefficients were adjusted for additional covariates using the competing risks multivariate model, the protective effect of SSE disappeared and was not significant (HR = 1.18; 95% CI = 0.64 – 2.16, p = 0.60). (Table 3-5) Adding SSE to other base models with comparable fits to the data, as well as to the null model with no covariates, showed similar estimates and p-values (data not shown).

Although there was a decreased risk of melanoma death for individuals who were performing other types of screening (vs. SSE) in the univariate analyses, when adjusted for other covariates the protective effect was modest and not significant. There was a slight decreased hazard of melanoma death for individuals who had 'At least one type of skin exam' (HR = 0.96, 95% CI = 0.67 – 1.38, p = 0.83) and 'Performed any casual skin exam' (HR = 0.93, 95% CI = 0.66 – 1.32, p = 0.69). Physician skin examination did not show a protective or significant effect when adjusted for covariates and competing risks (HR = 1.01, 95% CI = 0.71 – 1.45, p = .95). 'No skin exam' had a slightly increased estimated risk of melanoma death when adjusted for other covariates (HR = 1.07, 95% CI = 0.76 – 1.5, p = 0.69).

The association between Breslow depth and the risk of melanoma death decreased slightly after adjusting for covariates; however the strong statistically significant association was retained. (Table 3-5) As Breslow depth increased by one unit (mm) the risk of melanoma death increased by 21 percent (HR = 1.21, 95% CI = 1.13 – 1.29, $p < 0.001$). Poorer survival was also significantly associated with any mitoses in the multivariate competing risks regression model (HR = 2.06, 95% CI = 1.35 – 3.16, $p < 0.001$). Skin awareness was independently associated with decreased risk of melanoma death in the presence of competing risks (HR, 0.49; 95% CI, 0.31 – 0.77, $p = 0.002$). Nodular melanoma lost the strong association with the risk of dying from melanoma when adjusted for covariates; however, it remained to have the poorest survival of all histologic subtypes ((HR, 0.45; 95% CI, 0.27 – 0.73, $p = 0.001$).

DISCUSSION

Public health programs often use SSE as a component for skin cancer early detection and prevention programs; however, the long term effects of routine SSE have not been established.[12] Our study found that individuals who did not perform SSE experienced a continuous increase in the risk of melanoma death for nearly 20 years after diagnosis, whereas individuals who were performing SSE had a lower risk of melanoma death in the presence of competing risks and the risk of melanoma death plateaued at 10 years

post-diagnosis. In the univariate analysis, the hazard for melanoma death for those who performed SSE was 75 percent of the hazard for those who did not perform SSE. However, after adjusting for covariates in the multivariate model, the observed protective effect of SSE was not retained. Similar results were seen for skin exams conducted by a significant other or if skin exams were considered casual (rather than deliberately and purposefully). Several authors have not found a correlation between the length of time between first noticing a lesion and Breslow thickness[25-27] and it is possible that our lack of association between SSE and improved survival is a result of this phenomenon. Also, screening variables occurred infrequently, which may have resulted in low power to detect a statistically significant association.

Another SSE approach recommended by the American Academy of Dermatology and the American Cancer Society is the combination of SSE and skin exam by a clinician. Friedman et al.[28] and Aitken et al.[6] suggest that both forms of skin examination operate in synergy, with the physician encouraging SSE and if something suspicious results from the SSE to return to the physician. In a community based screening program, Aitken et al. had a 2.5-fold increase in participation by promoting skin self-examination in conjunction with whole body examination by a doctor.[6] Oliveria et al. found that nurse-delivered intervention is effective at increasing patient adherence with SSE.[29] Recently, researchers in Germany found that a skin cancer screening program implemented in Schlewig-Holstein was related to a 47-49% decrease in melanoma mortality that was not

seen in neighboring areas.[30] We found that individuals who had skin examinations by a physician had a lower estimated risk of melanoma death, although not significant. (HR = 0.88, 95% CI = 0.62 – 1.24, *p* = 0.46). Again, there was low power for this test due to small numbers.

We found that the risk of melanoma death increased as the thickness of the melanoma increased. Breslow depth as an independent predictor of melanoma survival has been well established.[31-33] Over time, the proportion of cases being diagnosed at later, less treatable stages has not improved. Rates for thick tumors (> or = 4 mm) increased statistically significantly (P =.0003) in males aged 60 years and older.[34] We analyzed survival patterns by histologic subtype since thick lesions are predominantly nodular melanoma[35] and nodular melanoma accounts for a disproportionate fraction of ultimately fatal cases compared with incident cases.[36] In our study population, 46.8 percent of the thick lesions were nodular histologic subtype. Individuals who had this subtype were statistically significantly more likely to die from melanoma compared to other subtypes in the univariate analysis; however, did not retain this association after being entered into the multivariate model.

Our results for skin awareness verified the findings of Berwick et al. that skin awareness is also a strong and independent predictor of survival of patients with melanoma and is a plausible indicator of likelihood of detecting melanoma early.[21] Skin awareness was

measured by asking, “Prior to your biopsy, did you ever think about your skin, how it looked or whether there were any changes; whether there were any abnormal marks?” After controlling for covariates skin awareness retained its strong and independent association with melanoma death. Skin awareness is an essential component of SSE. One must have a ‘baseline’ of their skin in order to ascertain whether or not a mark has changed over time and what would constitute a suspicious change. Robinson et al. found that individuals who perceived that they were at higher risk for developing melanoma were more likely to perform SSE.[10] In a pilot study where nurse provided education about melanoma, subjects were more likely to perform SSE at optimal levels (p=0.006).[7] Our study found that individuals who had skin awareness were more likely to perform SSE (OR= 2.81 CI: 1.77 - 4.46). Independent of SSE, individuals who were more aware of changes in their skin had a statistically Gray’s test for equality showed that the cumulative incidence curves for skin awareness (Y/N) were statistically different ($p < 0.001$) for death due to melanoma in the presence of competing risks.

A strength of this study was the thoroughness of long term follow-up. Research staff carefully followed individuals for several years, sending them follow-up surveys and address requests. Historical addresses made it easier to find people through the study period. To avoid possible misclassification, cause of death was carefully collected and reviewed using the CTR and NDI. Additionally, notes from physicians, notes from family members, notes from the interview, and obituaries were consulted if available. If a

cause of death did not coincide with information collected throughout the study, we asked staff at the CTR to review medical records that were available (e.g., pathology report, tumor abstract) to provide us with the best cause of death.

Interestingly, there was also a difference between individuals performing SSE and estimated risk of other causes of death ('other deaths'), although not statistically significant (p=0.25). Over time, the cumulative incidence of death from other causes was consistently higher for individuals who were not performing SSE compared to those who were performing SSE (data not shown). These data suggest that SSE may be associated with a healthier lifestyle in general.

By using the competing risks approach we were able to examine death from melanoma compared to death from other cause and we were able to study the covariate effects on the cumulative incidence function of death due to melanoma. Competing risks occur frequently in cancer research, particularly in long term survival studies, where there are many other factors that may cause death and must be handled appropriately in the analysis.[37-39]

In conclusion, we were able to examine the association between SSE and survival for nearly 20 years after an individual was diagnosed with melanoma. Although we could

not find a significant association between melanoma mortality and SSE when adjusting for competing risks and other covariates, we have confirmed previous results that increased skin awareness is related to better survival. Perhaps more public and provider awareness is needed before we can expect that SSE will show definite improvements in survival.

TABLE 3-1: COMPARISON OF SKIN SELF-EXAMINERS (SSE) AND NON-SKIN SELF-EXAMINERS (NO SSE) BY PATIENT CHARACTERISTICS

	no SSE		SSE	
Characteristic	#	%	#	%
Sex				
Male	307	54.4%	36	41.9%
Female	257	45.6%	50	58.1%
Education				
H.S. and less	223	39.5%	25	29.1%
More than H.S.	341	60.5%	61	70.9%
Stage				
Localized	542	96.0%	82	95.4%
Regional	11	2.0%	2	2.3%
Distant	11	2.0%	2	2.3%
Age Group (years)				
< 30	24	4.3%	7	8.1%
30-39	78	13.8%	17	19.8%
40-49	102	18.1%	17	19.8%
50-59	118	20.9%	17	19.8%
60-69	110	19.5%	19	22.1%
≥ 70	132	23.4%	9	10.4%

TABLE 3-2: CUMULATIVE MELANOMA MORTALITY RATES ADJUSTED FOR COMPETING RISKS STRATIFIED BY SKIN SELF-EXAMINATION (SSE) STATUS

	Incidence Estimates for Melanoma Death at Selected Time Points		
SSE Status	5 years CMR (95% CI)*	10 years CMR (95% CI)*	15 years CMR (95% CI)*
No SSE	0.15 (0.12 - 0.18)	0.19 (0.16 - 0.23)	0.21 (0.18 - 0.25)
SSE	0.12 (0.06 - 0.20)	0.17 (0.10 - 0.25)	0.17 (0.10 - 0.25)

CMR: Cumulative mortality rate estimates; CI: Pointwise 95% Confidence Intervals

TABLE 3-3: CUMULATIVE MELANOMA MORTALITY RATES ADJUSTED FOR COMPETING RISKS STRATIFIED BY TYPE OF SKIN EXAM, LONG TERM FOLLOW-UP

Type of Exam	5 years CMR (95% CI)		10 years CMR (95% CI)		15 years CMR (95% CI)	
No skin exam	0.16	(0.13 - 0.21)	0.21	(0.17 - 0.26)	0.24	(0.19 - 0.28)
Casual skin exam	0.14	(0.1 - 0.18)	0.17	(0.13 - 0.22)	0.18	(0.14 - 0.23)
SSE / Spouse / M.D. exam	0.12	(0.09 - 0.16)	0.17	(0.13 - 0.21)	0.18	(0.15 - 0.23)
SSE	0.12	(0.12 - 0.18)	0.17	(0.16 - 0.23)	0.17	(0.17 - 0.25)

CMR: Cumulative Mortality Rate Estimates; SSE: Skin self-examination; CI: Confidence Intervals

TABLE 3-4: UNIVARIATE ANALYSIS OF SELECT FACTORS ASSOCIATED WITH MELANOMA DEATH, COMPETING RISKS REGRESSION

Characteristic	HR	95% CI	*Nominal p*
Male gender	1.58	1.12 - 2.23	0.010
Age (years)	1.01	1.00 - 1.02	0.018
College education or more	0.68	0.49 - 0.95	0.024
Smoker	1.00	0.99 - 1.01	0.230
High knowledge melanoma symptoms	0.77	0.55 - 1.08	0.130
Skin awareness	0.49	0.32 - 0.76	0.001
Comorbidities (See appendix)	1.07	0.99 - 1.16	0.082
Solar elastosis	0.54	0.38 - 0.75	0.000
High sun exposure 10 yrs prior to diagnosis	0.91	0.85 - 0.96	0.002
High number of freckles	0.54	0.34 - 0.84	0.007
High number of burns	0.6	0.41 - 0.88	0.009
Total high sun exposure	0.95	0.92 - 0.99	0.006
Severe burn pain	0.72	0.51 - 1.02	0.061
Large nevi	1.03	0.99 - 1.07	0.200
Total nevi	1.00	0.99 - 1.01	0.200
Any type of skin exam (casual, deliberate)	0.75	0.54 – 1.05	0.092
No skin exams	1.34	0.95 – 1.87	0.092
Screener (See appendix)	0.64	0.36 – 1.13	0.130
Casual skin examiner	0.78	0.55 – 1.09	0.140
At least one type of skin exam	0.80	0.57 – 1.12	0.190
Skin self examiner	0.75	0.43 – 1.32	0.320
Physician exam	0.88	0.62 – 1.24	0.460
Spouse/other examiner	1.04	0.76 – 1.43	0.790
Went to dr for particular mark	1.42	1.02 – 1.99	0.039
Lentigo maligna	0.47	0.26 - 0.87	0.017
Breslow depth (mm)	1.31	1.23 - 1.39	0.000
Any mitoses	3.11	2.07 - 4.67	0.000
Any ulceration	2.89	1.97 - 4.23	0.000
Superficial spreading melanoma	0.40	0.28 - 0.56	0.000
Nodular melanoma	2.19	1.40 - 3.43	0.001

HR, Hazard Ratio; CI, Confidence Interval

TABLE 3-5: MULTIVARIATE ANALYSIS OF FACTORS* ASSOCIATED WITH MELANOMA DEATH, COMPETING RISKS REGRESSION

Characteristic	HR	95% CI	*p*
Age (years)	1.004	0.99 – 1.02	0.57
Skin awareness	0.49	0.31 – 0.77	0.002
Comorbidities (See appendix)	1.04	0.94 – 1.15	0.45
Skin self-exam (SSE)	1.18	0.64 – 2.16	0.60
Lentigo maligna	0.23	0.12 – 0.45	<.0001
Breslow depth (mm)	1.21	1.13 – 1.29	<.0001
Any mitoses	2.06	1.35 – 3.16	.0008
Superficial spreading melanoma	0.30	0.20 – 0.45	<.0001
Nodular melanoma	0.45	0.27 – 0.73	<.0001

HR, Hazard Ratio; CI, Confidence Interval
*Factors are adjusted for all other factors in the model.

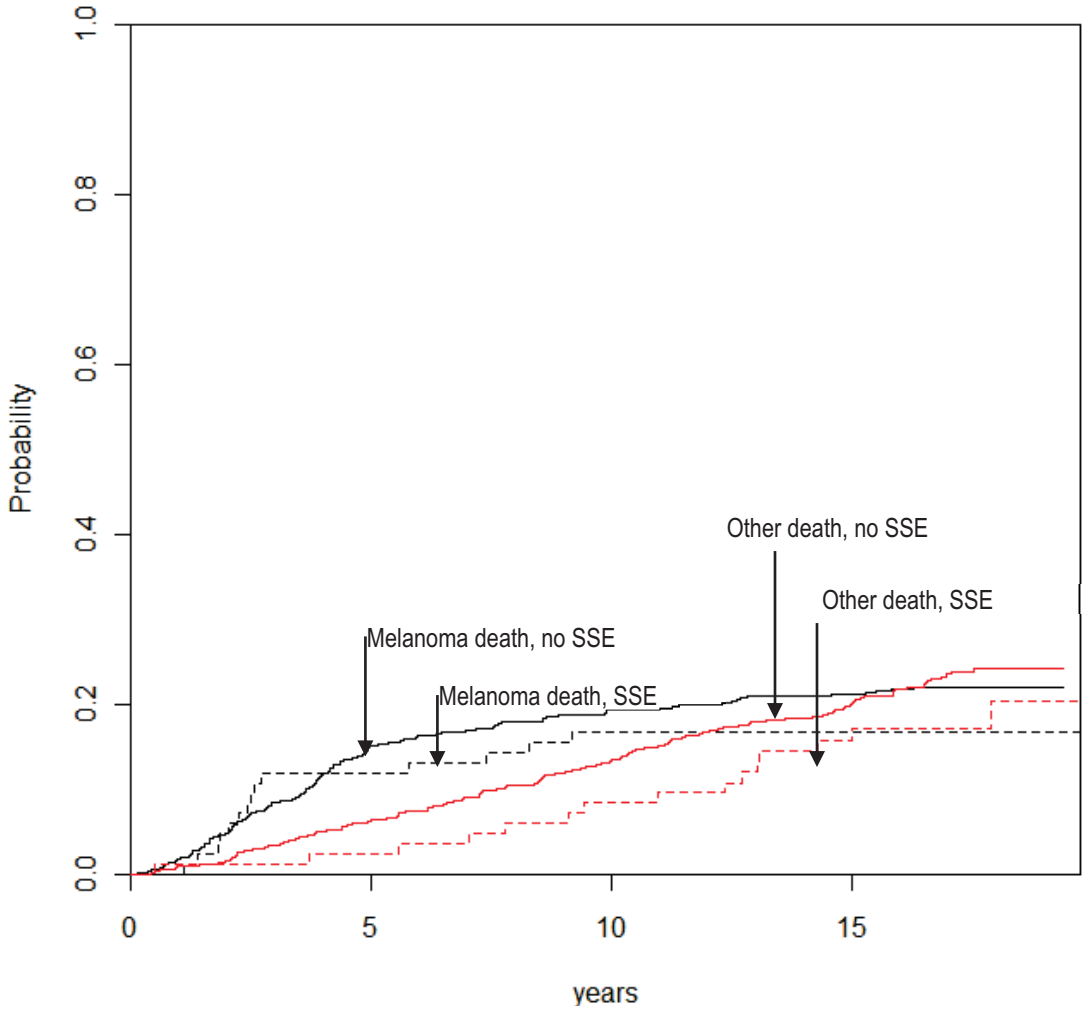


FIGURE 3-1: Estimated cumulative incidence curves with melanoma death and other causes of death as competing events for skin self-examiners (sse) and non-skin examiners (no sse). Gray's test for equality between sse and no sse was p=0.32.

REFERENCES

(1) Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association 1999; 94(446), 496-509.

(2) American Cancer Society. Cancer Facts & Figures 2012. Atlanta, GA: American Cancer Society, 2012.

(3) National Cancer Institute. Screening for Skin Cancer (PDQ). Bethesda, MD, National Cancer Institute, 1998.

(4) American Cancer Society. Cancer Facts & Figures 2006. Atlanta, GA: American Cancer Society, 2006.

(5) Berwick M, Wiggins C. The current epidemiology of cutaneous malignant melanoma. Frontiers in Bioscience 2006; 11:1244-1254.

(6) Aitken JF, Elwood JM, Lowe JB, Firman DW , Balanda KP, Ring IT. A randomised trial of population screening for melanoma. Journal of Medical Screening 2002; 9(1):33-37.

(7) Berwick M, Oliveria S, Luo ST, Headley A , Bolognia JL. A pilot study using nurse education as an intervention to increase skin self-examination for melanoma. Journal of Cancer Education 2000; 15(1):38-40.

(8) Friedman LC, Bruce S, Webb JA, Weinberg AD, Cooper HP. Skin self-examination in a population at increased risk for skin cancer. American Journal of Preventive Medicine 1993; 9(6):359-364.

(9) Koh HK, Miller DR, Geller AC, Clapp RW, Mercer MB, Lew RA. Who discovers melanoma? Patterns from a population-based survey. Journal of the American Academy of Dermatology 1992; 26(6):914-919.

(10) Robinson JK, Rigel DS, Amonette RA. What promotes skin self-examination? Journal of the American Academy of Dermatology 1998; 38(5 Pt 1):752-757.

(11) Girgis A, Campbell EM, Redman S, Sanson-Fisher RW. Screening for melanoma: a community survey of prevalence and predictors. Medical Journal of Australia 1991; 154(5):338-343.

(12) Wolff T, Tai E, Miller T. Screening for skin cancer: an update of the evidence for the U.S. Preventive Services Task Force. Annals of Internal Medicine 2009; 150(3):194-198.

(13) Oliveria S, Dusza S, Berwick M. Issues in the epidemiology of melanoma. Expert Review of Anticancer Therapy 2001; 1(3):453-459.

(14) Miller DR, Geller AC, Wyatt SW, Halpern A, Howell JB, Cockerell C et al. Melanoma awareness and self-examination practices: results of a United States survey. Journal of the American Academy of Dermatology 1996; 34(6):962-970.

(15) Hill D, White V, Borland R, Cockburn J . Cancer-related beliefs and behaviours in Australia. Australian Journal of Public Health 1991; 15(1):14-23.

(16) Balanda KP, Lowe JB, Stanton WR, Gillespie AM. Enhancing the early detection of melanoma within current guidelines. Australian Journal of Public Health 1994; 18(4):420-423.

(17) Del Mar CB, Stanton WR, Gillespie AM, Lowe JB, Balanda KP. What use do people make of physicians in checking their skin for cancer? Cancer Detection & Prevention 1996; 20(4):325-331.

(18) Manson JE, Rexrode KM, Garland FC, Garland CF, Weinstock MA. The case for a comprehensive national campaign to prevent melanoma and associated mortality. Epidemiology 2000; 11(6):728-734.

(19) Weinstock MA. Progress and prospects on melanoma: the way forward for early detection and reduced mortality. Clinical Cancer Research 2006; 12(7 Pt 2):2297s-2300s.

(20) Berwick M, Begg CB, Fine JA, Roush GC, Barnhill RL. Screening for cutaneous melanoma by skin self-examination. Journal of the National Cancer Institute 1996; 88(1):17-23.

(21) Berwick M, Armstrong BK, Ben Porat L, Fine J, Kricker A, Eberle C et al. Sun exposure and mortality from melanoma. Journal of the National Cancer Institute 2005; 97(3):195-199.

(22) Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. The Annals of Statistics 1988; 16(3): 1141-1154.

(23) Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases 1987; 40(5):373-383.

(24) Scrucca L, Santucci A, Aversa F. Regression modeling of competing risk using R: an in depth guide for clinicians. Bone Marrow Transplantation 2010; 45(9):1388-1395.

(25) Baade PD, English DR, Youl PH, McPherson M, Elwood JM, Aitken JF. The relationship between melanoma thickness and time to diagnosis in a large population-based study. Archives of Dermatology 2006; 142(11):1422-1427.

(26) Lipsker DM, Hedelin G, Heid E, Grosshans EM, Cribier BJ. Striking increase of thin melanomas contrasts with stable incidence of thick melanomas. Archives of Dermatology 1999; 135(12):1451-1456.

(27) Berwick M. Evaluating early detection in the diagnosis of melanoma. Archives of Dermatology 2006; 142(11):1485-1486.

(28) Friedman RJ, Rigel DS, Silverman MK, Kopf AW, Vossaert KA. Malignant melanoma in the 1990s: the continued importance of early detection and the role of physician examination and self-examination of the skin. Ca: a Cancer Journal for Clinicians 1991; 41(4):201-226.

(29) Oliveria SA, Dusza SW, Phelan DL, Ostroff JS, Berwick M, Halpern AC. Patient adherence to skin self-examination: effect of nurse intervention with photographs. American Journal of Preventive Medicine 2004; 26(2): 152-155.

(30) Katalinic A, Waldmann A, Weinstock MA, Geller AC, Eisemann N, Greinert R et al. Does Skin Cancer Screening Save Lives? Cancer 2012; epub ahead of print[doi: 10.1002/cncr.27566]: 1-8.

(31) Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. Journal of Clinical Oncology 2001; 19(16):3622-3634.

(32) Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR et al. Final version of 2009 AJCC melanoma staging and classification. Journal of Clinical Oncology 2009; 27(36):6199-6206.

(33) Morton DL, Davtyan DG, Wanek LA, Foshag LJ, Cochran AJ. Multivariate analysis of the relationship between survival and the microstage of primary melanoma by Clark level and Breslow thickness. Cancer 1993; 71(11):3737-3743.

(34) Jemal A, Devesa SS, Hartge P, Tucker MA . Recent trends in cutaneous melanoma incidence among whites in the United States. Journal of the National Cancer Institute 2002; 93(9):678-683.

(35) Chamberlain AJ, Fritschi L, Giles GG, Dowling JP, Kelly JW. Nodular type and older age as the most significant associations of thick melanoma in Victoria, Australia. Archives of Dermatology 2002; 138(5):609-614.

(36) Shaikh WR, Xiong M, Weinstock MA. The contribution of nodular subtype to melanoma mortality in the United States, 1978 to 2007. Archives of Dermatology 2012; 148(1):30-36.

(37) Satagopan JM, Ben Porat L, Berwick M, Robson M, Kutler D, Auerbach AD . A note on competing risks in survival data analysis. British Journal of Cancer 2004; 91(7):1229-1235.

(38) Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. Clinical Cancer Research 2007; 13(2 Pt 1):559-565.

(39) Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. American Journal of Epidemiology 2009; 170(2):244-256.

APPENDIX 3-1: DEVELOPMENT OF INDICES USED IN ANALYSIS

COMORBIDITIES INDEX

The purpose of this exercise was to create a comorbidity score for each subject, as the total number of comorbid conditions can be a predictor of mortality.(Charlson et al., 1987) A comorbidity index was developed based on the responses to the survey question, "Has a doctor ever told you that you had any of the following?" The level of severity was gauged on the response to the question, "[IF YES] Were you hospitalized for this?" As the comorbidity index was developed post-hoc, a method similar to the Charlson weighted index of comorbidity was adapted for use.[23] The adjusted relative risks employed by Charlson et. al were used as weights for the different comorbid diseases that were reported by the subject. The level of severity was determined by hospitalization. If the person was hospitalized for the condition, the relative risk value for the more severe category was used as the weight. For instance, the renal category has adjusted relative risks for two levels of severity: mild and moderate-severe. If the subject had the condition, but was not hospitalized, the relative risk related to mild level of disease was used. If the subject was hospitalized for the condition the relative risk for the more severe level of disease was used. If two levels of severity were not specified in the Charlson index, the same relative risk value would be used for individuals who were and were not hospitalized for the condition. The exact relative risks for each comorbid condition by severity level were summed and rounded to the first decimal place to produce a weighted comorbidity score for each subject. For instance, a person who

reported asthma (1.3), stroke (1.4), and being hospitalized with pneumonia (1.4) had a comorbidity score of 4.1.

Table 3-6 shows the mapping process that was used to determine how each survey item was weighted using the Charlson adjusted relative risks based on condition and severity. Although our survey did not assess the entire comorbidity index proposed by Charlson et al, eight of the ten categories were represented. The comorbidity index included the following conditions: tuberculosis, stroke, hypertension, emphysema, chronic bronchitis, pneumonia, chronic lymphocytic leukemia, Hodgkin lymphoma, rheumatoid and other arthritis, lupus, thyroiditis, asthma, diabetes, kidney problems, liver problems, heart disease, and cancers other than melanoma. There were six conditions that were measured on the survey, but were not included in the final comorbidity index. Repeated Strep infections of the throat, tonsillitis, shingles, fungal infections, and any other medical conditions did not have a weight specified on the Charlson index. All individuals had malignant melanoma, thus this condition was not part of the score. Thus, the comorbidity score could range from 0 to 33.4 SAS version 9.1 was used to create the comorbidity score for each subject. The mean number of comorbid diseases per subject was 2.60 (± 1.87 SD), with a range of 0- 10. The weighted comorbidity score had a mean of 1.96 (±2.03 SD) with a range of 0 to 11. Frequency distribution of scores is shown in Table 3-7.

TABLE 3-6: WEIGHTS USED FOR COMORBID CONDITIONS BASED ON CHARLSON WEIGHTED INDEX OF COMORBIDITY

Answered yes to "Has a doctor ever told you that you had any of the following…"	ARR	If also hospitalized for condition, then use this ARR*	Charlson Category
Tuberculosis	1.3	1.4	pulmonary- mild, pulmonary- severe moderate
Stroke	1.4	1.4	vascular- cerebrovascular
Hypertension	1.0	1.0	vascular- hypertension
Emphysema	1.3	1.4	pulmonary- mild, pulmonary- severemoderate
Chronic bronchitis	1.3	1.4	pulmonary- mild, pulmonary- severemoderate
Pneumonia	1.3	1.4	pulmonary- mild, pulmonary- severemoderate
Chronic lymphocytic leukemia	2.2	2.2	cancer
Hodgkin's disease	2.4	2.4	cancer
Rheumatoid Arthritis	1.4	1.4	miscellaneous- rheumatologic
Other arthritis	1.4	1.4	miscellaneous- rheumatologic
Lupus	1.4	1.4	miscellaneous- rheumatologic
Thyroiditis	1.2	1.2	endocrine- other endocrine
Asthma	1.3	1.4	pulmonary- mild, pulmonary- severemoderate
Diabetes	1.4	1.9	endocrine- diabetes, endocrine- diabetes with end organ
Problems with kidneys	0.5	1.5	renal- mild, renal-moderate to severe
Problems with liver	1.4	2.9	liver- mild, liver-moderate to severe
Heart attack, angina, or coronary artery disease	0.6	1.4	myocardial infarction
Gastrointestinal cancer	2.1	2.1	cancerous tumor
Respiratory cancer	2.1	2.1	cancerous tumor
Other cancer	2.1	2.1	cancerous tumor
Conditions measured on survey, but were not included in final comorbidity index			
Repeated Strep Infections of the throat			
Tonsillitis			
Shingles (herpes zoster)			
Any other medical conditions that you think we should know about? Specify.			
Malignant melanoma			
Fungal infections			

*ARR = Adjusted Relative Risk values from Charlson (1987)[23]

TABLE 3-7: FREQUENCY DISTRIBUTION OF COMORBIDITY SCORES

Weight	COUNT	PERCENT
0	207	31.84
0.5	2	0.30
0.6	1	0.15
1	48	7.38
1.2	5	0.76
1.3	36	5.53
1.4	60	9.23
1.5	8	1.23
1.6	1	0.15
1.8	2	0.30
1.9	1	0.15
2	2	0.30
2.1	22	3.38
2.2	2	0.30
2.3	10	1.53
2.4	38	5.84
2.5	3	0.46
2.6	5	0.76
2.7	14	2.15
2.8	16	2.46
2.9	3	0.46
3	2	0.30
3.1	4	0.61
3.3	1	0.15
3.4	6	0.92
3.5	14	2.15
3.6	5	0.76
3.7	12	1.84
3.8	13	2.00
3.9	4	0.61
4	6	0.92
4.1	2	0.30
4.2	10	1.53

Weight, con't	COUNT	PERCENT
4.3	1	0.15
4.4	2	0.30
4.5	13	2.00
4.7	2	0.30
4.8	6	0.92
4.9	3	0.46
5	4	0.61
5.1	4	0.61
5.2	4	0.61
5.3	5	0.76
5.4	3	0.46
5.5	1	0.15
5.6	1	0.15
5.7	4	0.61
5.8	3	0.46
5.9	5	0.76
6	2	0.30
6.1	1	0.15
6.2	1	0.15
6.3	1	0.15
6.5	1	0.15
7	1	0.15
7.1	2	0.30
7.2	4	0.61
7.3	1	0.15
8	1	0.15
8.1	1	0.15
8.4	1	0.15
9.1	1	0.15
9.4	1	0.15
9.5	1	0.15
10.3	1	0.15
10.7	1	0.15
10.9	1	0.15
11	1	0.15

SCREENING INDEX

This weight was created to provide weights for individuals who used health care screening as part of their normal healthcare routine to account for individuals who were habitual screeners. More weight was given to individuals who had multiple screenings over the course of their lifetime. A comorbidity index was developed based on the responses to the survey questions:

- Have you ever had tests of your large bowel? If yes, what did you have…a barium enema? sigmoidoscopy? colonoscopy? Sigmoidoscopy or colonoscopy, not sure of type? (Yes/No response) If yes, were these done for routine checks, prevention, or diagnosis? Number of times?

- Approximately how often on average do you have a gynecologic exam with a pap smear? (Response = #per / # yrs.)

- Approximately how often on average do you have a breast exam by a doctor? (Response = #per / # yrs.)

- Have you ever had a mammogram, that is, an x-ray of your breast? (Yes/No) If yes, how many have you ever had?

- During the past year, did you examine your own breasts for lumps and other unusual conditions? (Yes/No) If yes, approximately how many times during the past year did you do a breast examination on yourself?

Screeners were recoded as high(2) or low(1) or no screeners(0) for each type of screening: mammography, breast self-exam, gynecologic exam, breast exam by a physician, barium enema, sigmoidoscopy, colonoscopy, and colonoscopy/sigmoidoscopy using the median value as the cutoff point. The values for each screening type were summed and divided by the number of screenings appropriate for each gender (Males=4, Females=8). SAS version 9.1 was used to create the screening score for each subject. The mean number of screenings per male subject was 0.94 (± 1.2 SD), with a range of 0 to 4. The mean number of screenings per female subject was 4.4 (± 1.9 SD), with a range of 0 to 11.

TABLE 3-8: HIGH AND LOW SCREENING CUTOFFS BY SCREENING TYPE

Screening Type	Low	High	Gender
Barium Enema	≤1	>1	M&F
Colonoscopy	≤1	>1	M&F
Sigmoidoscopy	≤1	>1	M&F
Unsure Colon/Sigmoid	≤1	>1	M&F
Breast Exam by MD	≤11	>11	F
Gynecologic Exam	≤11	>11	F
Mammography	0	≥1	F
Breast Self-Exam	0	≥1	F

M=Males, F=Females; Low and High screening values were determined using the median as the cutoff point.

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases 1987; 40(5):373-383.

CONCLUDING REMARKS

Over the course of this doctoral research, the importance of awareness has been a common thread running through all three of my studies.

When I first began my graduate studies, I attended a podium presentation about melanoma in Australia, the country with the highest melanoma rates in the world, where I learned about the massive public health campaigns to have everyone wear hats and sunscreen, to have classrooms equipped with sunscreen dispensers and hats, and to encourage people to stay indoors during the sunniest part of the day. Nearly 15 years later, the U.S. has made headway. The American Cancer Society uses the "Slip! Slap! Slop! and Wrap" campaign to encourage people to Slip on a shirt, Slop on sunscreen, Slap on a hat, and Wrap on sunglasses.[1] The Centers for Disease Control's (CDC) "Choose Your Cover" campaign, which concluded in 2003, encouraged people to protect themselves from the sun.[2] Several foundations, such as the Melanoma Research Foundation, the Skin Cancer Foundation, and the American Melanoma Foundation provide education about melanoma prevention on their websites and social media networks have made it easy to share educational information. Recently, policymakers have introduced the Melanoma Research Act of 2012 which proposes to designate existing funds from the tanning salon tax towards melanoma research.[3] In New Jersey, the Senate health committee just approved a bill (S1172) that bans people who are 15 and younger from using tanning salons and now it will move to the full Senate.[4]

Yet, studies conducted in the United States have found that most Americans, adults and children, do not follow recommended sun protection practices.[2] The National Health Interview Survey's Cancer Control Supplement found that 50 percent of people aged 18-29 suffered from at least one sunburn in the past year, despite an increase in sun protection. The most common protective behaviors reported in 2010 were using sunscreen (37%, CI = 34.7 – 39.5) and staying in the shade (34.9%, CI = 32.6 – 37.3).[5] Only 3 in 10 adults routinely practice sun-protection behaviors; and, among adolescents 69% were sunburned in the previous summer.[6] Indoor tanning use was highest among white women aged 18-21 years, with an average of 27.6 sessions per year.[7]

Our study on skin self-examination (SSE) and survival (Chapter 3) found that awareness for abnormal changes in the skin was related to improved survival. By being aware of their skin and performing regular self-examinations, people are more likely to notice changes that can possibly lead to earlier removal and proper treatment. Additionally, when analyzing the incidence data for childhood melanoma (Chapter 1), it is evident that adolescent females have a significantly higher incidence than adolescent males, and it is possible that the incidence gap may be starting as early as age 10. The U.S. young adult population is clearly a focus for skin awareness campaigns.

Through this research we found that the lack of melanoma awareness extends to medical professionals, as well. When studying melanoma incidence in children (Chapter 1) we found that children were diagnosed at later stages and with thicker lesions compared to adolescents and adults, indicating an area for improvement. Furthermore, our study on under- and late- reporting (Chapter 2) demonstrated that many providers were not aware of reporting requirements. It is likely that the childhood and adolescent rates were distorted by underestimation. Accurate incidence rates and trends are necessary to focus public health efforts in the future.

It is evident through these research projects, and through important research being done world-wide, that more public health efforts are needed to continue raising melanoma awareness. By increasing public and provider awareness, we have the potential to increase the value of screening and surveillance to continue reducing the burden of melanoma.

REFERENCES

(1) American Cancer Society. Skin Cancer Prevention and Early Detection. Atlanta, GA: American Cancer Society, 2011.

(2) Jorgensen CM, Wayman J, Green C, Gelb CA. Using health communications for primary prevention of skin cancer: CDC's Choose Your Cover campaign. Journal of Womens Health & Gender-Based Medicine 2000; 9(5):471-475.

(3) Bilbray B, Maloney C. Melanoma Research Act of 2012. Briefing June 27, 2012.

(4) Weinberg L, Singer R. Bill Number S1172. 2012. State of New Jersey, 215th Legislature.

(5) Centers for Disease Control and Prevention. Sunburn and sun protective behaviors among adults aged 18-29 years--United States, 2000-2010. MMWR - Morbidity & Mortality Weekly Report 2012; 61(18):317-322.

(6) Buller DB, Cokkinides V, Hall HI, Hartman AM, Saraiya M, Miller E et al. Prevalence of sunburn, sun protection, and indoor tanning behaviors among Americans: review from national surveys and case studies of 3 states. Journal of the American Academy of Dermatology 2011; 65(5 Suppl 1):S114-S123.

(7) Centers for Disease Control and Prevention. Use of indoor tanning devices by adults--United States, 2010. MMWR - Morbidity & Mortality Weekly Report 2012; 61(18):323-326.

LISA E. PADDOCK
CURRICULUM VITAE

FULL NAME: Lisa Erin Paddock (née McCartney)

EDUCATION:

2012 ***Doctor of Philosophy,*** *Epidemiology*
University of Medicine & Dentistry of New Jersey, School of Public Health, Piscataway, NJ
And
Rutgers, The State University of New Jersey, Graduate School, New Brunswick, NJ

2000 ***Master of Public Health,*** *Epidemiology & Quantitative Methods*, University of Medicine & Dentistry of New Jersey, School of Public Health, Piscataway, NJ

1997 ***Bachelor of Science,*** Biobehavioral Health,
The Pennsylvania State University, University Park, PA

PROFESSIONAL POSITIONS

Dec 2002 – present
RESEARCH SCIENTIST 2
Cancer Epidemiology Program, New Jersey State Cancer Registry, A Program of The New Jersey Department of Health and The Cancer Institute of New Jersey, Hamilton, NJ.

Feb 2001 – Dec 2002
RESEARCH SCIENTIST 3
Office of Cancer Control & Prevention, NJ Department of Health, Trenton, NJ.

July 1999 – Feb 2001
ASSISTANT PROJECT DIRECTOR, *School of Population Health (Formerly the Office of Health Policy and Clinical Outcomes), Thomas Jefferson University, Philadelphia, PA.*

Nov 1997 – July 1999
RESEARCH STUDY COORDINATOR, *School of Population Health (Formerly the Office of Health Policy and Clinical Outcomes), Thomas Jefferson University, Philadelphia, PA.*

Sept – Nov 1997
RESEARCH ASSOCIATE, *French Clinical Trials Team, IMS-America (Formerly DataEdge, LLC), Fort Washington, PA.*

PROFESSIONAL APPOINTMENTS

2007	INSTITUTIONAL REVIEW BOARD MEMBER, *New Jersey Department of Health*
2004	ADVISORY BOARD FOR NOVARTIS OUTREACH AND EDUCATION PROJECT (NOEP) *Cancer Institute of New Jersey, New Brunswick, NJ*
2001-2002	MELANOMA AND SKIN CANCER COALITION Governor's Task Force on Cancer Prevention, Early Detection and Treatment in NJ
2001	CANCER ACTION TEAM OF THE COMMUNITY HEALTH TRUST *St. Clare's Health System, NJ*

ORIGINAL PAPERS

Gifkins D, Olson SH, **Paddock L**, King M, Demissie K, Lu SE, Kong AN, Rodriguez-Rodriguez L, Bandera EV. "Total and individual antioxidant intake and risk of epithelial ovarian cancer." BMC Cancer 2012, 12(1):211.

Bandera EV, King M, Chandran U, **Paddock LE**, Rodriguez-Rodriguez L, Olson SH. "Phytoestrogen consumption from foods and supplements and epithelial ovarian cancer risk: a population-based case control study." BMC Women's Health 2011, 11:40-48.

Buller DB, Cokkinides V, Hall HI, Hartman AM, Saraiya M, Miller E, **Paddock LE**, Glanz K. "Prevalence of Sunburn, Sun Protection, and Indoor Tanning Behaviors Among Americans: Review from National Surveys and Case Studies of Three States." Journal of the American Academy of Dermatology. 2011, 65: 114-123.

Chandran U, Bandera EV, Williams-King MG, **Paddock LE**, Rodriguez-Rodriguez L, Lu SE, Faulkner S, Pulick K, Olson SH. "Healthy eating index and ovarian cancer risk." Cancer Causes Control. Apr 2011, 22(4):563-71. Epub 2011 Feb 1.

Paddock LE, Veloski J, Chatterton ML, Gevirtz FO, Nash DB. "Development and Validation of a Questionnaire to Evaluate Patient Satisfaction With Diabetes Disease Management." Diabetes Care. July 2000, 23: 951-956.

Paddock LE, Phillips A, Chodoff P. "Quality Improvement Tools in Disease Management." Disease Management. 2001, (6)1;63-69.

Xu G, **Paddock LE**, O'Connor JP, Nash DB, Zitter M. "Chief Medical Officers' Perceptions of Disease Management." Disease Management. 2001, 4(1): 19-24.

Lofland JH, Touch S, O'Connor JP, Chatterton ML, Moxey E, **Paddock LE**, Touch S., Desai S. Palivizumab (Synagis®) for RSV Prophylaxis of High-Risk Infants: A Cost-Effectiveness Analysis. Clinical Therapeutics. 2000, 22(11): 1357-1369.

McCartney LE, Kim SS, Gevirtz FO. "Questionnaire Development Part III: A Practical Application." Pharmacy & Therapeutics. October 1999, 24(10): 472-479.

Gevirtz FO and **McCartney LE**. "Questionnaire Development, Part II: Reliability, Validity and Responsiveness." Pharmacy & Therapeutics. September 1999, 24(9): 431-436.

McCartney LE, Gevirtz FO. "Questionnaire Development 101: The Basics." Pharmacy & Therapeutics. August 1999, 24(8): 386-389.