INCIDENCE OF MALIGNANT MELANOMA BY ANATOMIC SITE, GENDER, AND GEOGRAPHIC LOCATION:

AN UNANTICIPATED TREND

by

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THESIS

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CERTIFICATE OF APPROVAL

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Abbreviations

AAC UVI	Annual average cumulative ultraviolet index
β	Regression coefficient
BCC	Basal cell carcinoma
CI	Confidence interval
EPA	U.S. Environmental Protection Agency
MM	Malignant melanoma
MEM	Mixed effects model
MED	Minimal erythema dose
mJ	MilliJoule
NCI	National Cancer Institute
nm	Nanometer
p	Probability
r	Correlation coefficient
R^2	Correlation coefficient squared
SAA	Surface area adjustment
SEER	Surveillance, Epidemiology, and End Results Program
SCC	Squamous cell carcinoma
SLR	Simple linear regression
USDA	United States Department of Agriculture
UVA	Ultraviolet spectrum A
UVB	Ultraviolet spectrum B
UVC	Ultraviolet spectrum C

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Dedication

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Abstract

The incidence of malignant melanoma has increased over the past 60 years in the United States. Since the early 1950s, evidence has been accumulating to link solar ultraviolet (UV) radiation to melanoma and it is now commonly accepted as a causal factor. Patterns of exposure to solar UV radiation and sun burns may contribute dissimilarly to the risk levels for malignant melanoma (MM) by gender at different anatomic sites. The head may be covered by hats and hair; the arm & shoulder, trunk, and leg & hip may be covered by clothing. Additionally, sun screen may be differentially applied to these areas of the body. The objective of this research is to generate exposure-response relationships by anatomic site and gender. We performed an ecologic analysis using population-based data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute and UV Index data from the National Weather Service. The analysis was restricted to Caucasians less than 76 years of age whose MM was diagnosed during 2000-04 in 14 SEER Cancer Registries in the contiguous United States, not including Hawaii. Cases totaled 39,582. The exposure-response relationships by anatomic site were significantly different between men and women. Incidence of MM in males exceeded females' at all anatomic sites, except for the leg & hip. In linear regression analyses stratified by gender, age-adjusted incidence rates decreased with increasing average annual cumulative UV Index for all anatomic sites, except for male head (face, lip, eyelid, scalp, neck, ear) and male leg & hip. Incidence rates were lower in registries with greater annual cumulative UV Index days, suggesting that other

factors associated with geographic residence may now be playing a larger role in risk. Such as, skin cancer prevention awareness and protective behaviors having more success in the “Sun Belt”. Therefore, people living in northern latitudes of the US should be counseled regarding their potential increased risk of MM occurring in typically covered anatomic sites. They should avoid behavior that may increase the risk of MM, particularly intermittent sunburns. Providers in northern latitudes should be as suspicious of skin lesions on the trunk, shoulder & arm, and leg & hip as they would be in southern locations.

Chapter 1: Introduction

Background

In the 1970s and 1980s, invasive melanoma increased in the United States at a rate of over 52% per decade (Elder, 1995). Likewise, in Australia, the incidence of melanoma doubled in the 1960s and 1970s (Little, Holt, & Davis, 1980) and increased by another 35% in the 1980s (MacLennan, Green, McLeod, & Martin 1992). However, the survival rate (five-year) in the United States has increased from 10% in 1925 (Pack, Gerber, & Sharnagel, 1952) to more than a 71% survival rate (eight-year) in the 1970s (Clark et al., 1989), suggesting that earlier diagnosis has improved the case-fatality rate.

In the 1950s, McGovern (1952) was the first to hypothesize about an association between sunlight exposure and melanoma. A few years later, Lancaster (1956) tested the hypothesis, and published the first study associating latitude of residence and mortality rates of melanoma, using latitude of residence as a proxy for ambient UV radiation. Lancaster's (1956) findings supported the etiologic role of sun exposure for melanoma. Since the mid-1950s, epidemiologic studies have continued to demonstrate an association (Gellin, Kopf, & Garfinkel, 1969; Lee, 1975). Other studies have also explored the latitude gradient and the incidence of melanoma and found an association (Eide & Weinstock, 2005; Fears, Scotto, & Schneiderman, 1976; Hu, Ma, Collado-Mesa, & Kirsner, 2004; MacLennan, Kelly, Rivers, & Harrison, 2003).

Exposure - Ultraviolet Radiation

Sunlight is composed of electromagnetic energy described on the nanometer level (nm) (10^{-9} m) by wavelength (Scotto, Fears, & Fraumeni, 1996). The wavelengths of importance to this discussion are in the ultraviolet (UV) range. UV radiation spans from about 100nm to 400nm of the electromagnetic spectrum. UV radiation is further designated into three subgroups by photobiologic effect: UVC (< 280nm), UVB (280nm – 320nm), and UVA (320nm – 400nm) (Scotto et al., 1996). UVC is effective in inactivating cells and viruses; specifically they lose their ability to reproduce (Diffey, 1991). UVB is effective in producing skin erythema (sunburn) in humans. UVA can also produce skin erythema in humans, though it is three to four times less effective than UVB in doing so. Ozone, in the earth's stratosphere, fortunately absorbs a significantly large portion of UV radiation, estimates of the wavelengths absorbed by the ozone layer range from $\lambda < 290$nm to $\lambda < 310$nm (deGruijl & van der Leun, 2000; Fears, Scotto, & Schneiderman, 1976; Scotto et al., 1996).

The subgroup of UV radiation that will be focused on for this thesis is the UVB range. Diffey (1991) describes how each wavelength in the UVB range has its own minimal erythema dose (MED). That is, at each wavelength a different dose (in milliJoules, mJ) is required to cause minimal erythema or reddening of the skin. The most effective wavelengths for producing erythema are in the range of 305nm or less (Setlow, 1974). At 320nm, the effectiveness of UVB decreases to about 1% of the effectiveness at 297nm – 300nm (Diffey, 1991).

Ozone Depletion

It has been suggested that stratospheric ozone depletion may increase the levels of UV radiation hitting the earth's surface (deGruijl & van der Leun, 2000). Moan & Dahlback (1992) studied the association between the rise in incidence of skin cancer and ozone depletion. They concluded that ozone depletion was not the cause of the rise of incidence rates of skin cancer in Norway. Additionally, Bruhl & Crutzen (1989) estimated that reductions in the stratospheric ozone layer may be offset by increases in pollution in the troposphere in which UV radiation is more efficiently absorbed. The influence of ozone and the extent of its depletion in the coming decades is still contentious.

Measurement of UV Radiation

Measurement of UV radiation can be accomplished through a combination of satellite data and other forecasting equipment, and through surface measurements. The National Weather Service (NWS) under the National Oceanic Atmospheric Administration (NOAA) has developed a UV Index for 58 cities that is calculated using forecasted stratospheric ozone data, a radiative transfer model, forecasted cloud amounts, and the elevation of the forecast cities (www.cpc.ncep.noaa.gov).

UV radiation measurements via surface observations can be made using spectrophotometers. The Environmental Protection Agency (EPA) and the United States Department of Agriculture (USDA) have networks of sites to gather this data. The UV radiation measurements are calibrated to incorporate the

erythema action spectrum using the McKinlay-Diffey erythema action spectrum that weights the UV irradiances and integrates them over the 290-325nm range to calculate an erythema dose rate. The EPA meters are located at seven urban sites and fourteen National Park sites and there are 39 USDA meters located across the United States.

Outcome – Skin Cancer

The majority of research on skin cancer and sunlight has been done with Caucasian or white populations. This is due in part to the increase in risk for skin cancer for fair-skinned people compared to those with dark skin (Marrett, King, Walter, & From, 1992). In fact, incidence rates for skin cancer are estimated to be about five to thirty times higher among white populations compared to darker skinned populations (Cormier et al., 2006; Eide & Weinstock, 2005; Elder, 1995; Hu et al., 2004; Marks, 2000). Two recent studies found contradictory results regarding darker skinned populations. Hu et al. found a positive correlation between the incidence of melanoma in blacks and Hispanics and the UV Index, though it was only significant for black males (0.93, p=0.01). Alternatively, Eide & Weinstock found a negative correlation, though not significant, between the incidence of melanoma in blacks, Hispanics, and Asians and the UV Index. Also, unsurprisingly, a significant positive correlation was found between in non-Hispanic whites and the incidence of melanoma (r=0.85, p=0.001) in the Eide & Weinstock study. From this point forward, unless otherwise specified, we will

limit our discussion to Caucasian or whites, the group at greatest risk for malignant melanoma due to excess solar UV radiation exposure.

In 1976, the International Classification of Disease for Oncology (ICD-O) was developed, at which time the three main morphological types of cancer could then be separated for reporting and diagnostic purposes (Osterlind, Hou-Jensen, & Jensen 1988), specifically squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and melanoma. With this addition to the ICD-O code, in conjunction with the ability to systematically designate and record the location of melanomas, the distribution of skin cancer morphology by anatomic site was able to be examined. Concurrently, in the early 1970s, the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute began to track cancer incidence and survival in the United States in nine cities and/or states. The SEER registries now total 18, and encompass approximately 26 percent of the US population. In the SEER Program, only malignant melanoma is ascertained on a routine basis, due to the practical difficulties of outpatient diagnosis and treatment of SCC and BCC (e.g., lack of biopsy before cryotherapy) (www.seer.cancer.gov).

SCC, BCC, and melanoma have all been shown to have an association with sunlight (English, Armstrong, Kricker, & Fleming, 1997; Holman, Armstrong, & Heenan, 1986; Weinstock, 1996). Though over time, patterns of distribution by anatomic site and morphology have raised questions regarding differing etiologies and relationships with sun exposure. SCC has the most direct relationship with sunlight exposure (Rosso et al., 1996). The more total sun

exposure an individual has, the higher the risk of SCC. Whereas for BCC, the risk increases with increasing sun exposure, then it flattens (Kricker, Armstrong, English, & Heenan, 1995; Rosso et al., 1996; Strickland et al., 1989). Melanoma's relationship with sunlight appears to be determined not only by the amount of exposure, but also to the pattern of exposure (Elwood & Jopson, 1997; Katsambas & Nicolaidou, 1996; Nelemans et al., 1993).

Patterns of Exposure

The literature for pattern of exposure generally divides exposure into two groups, intermittent sun exposure and chronic sun exposure. It has been suggested that intermittent sun exposure to UV radiation is related to melanomas on anatomic sites that are typically uncovered during recreational activities or sunbathing, such as the trunk and lower limbs (Bulliard, Cox, & Elwood, 1997; Dal, Boldemann, & Lindelf, 2007). In that, unacclimatized skin exposed acutely to the sun is more susceptible to the initiation of melanoma (Elwood & Gallagher 1998). Likewise, chronic sun exposure to UV radiation is related to melanomas on anatomic sites that are typically uncovered all the time such as the face, ears and neck (for males only) (Bulliard et al., 1997; Osterlind et al., 1988), or exposed to chronic occupational sun exposure (Beral & Robinson, 1981). In a review by Elwood & Jopson (1997), it is also suggested that chronic exposure can offer protection for the skin related to tanning and skin thickening and melanomas on chronically exposed sites are related to an accumulation of

exposure, rather than acute intermittent exposure, though until recently this hypothesis had not been tested.

Whiteman et al. (2006) were one of the first groups to study sun exposure by anatomic site. They found that individuals with melanomas on the head and neck were more likely to report higher levels of sun exposure in adulthood than individuals with melanomas on the trunk (OR, 2.43; 95% CI: 0.98 - 5.99) and also report higher levels of occupational exposure in adulthood than individuals with melanomas on the trunk (OR, 3.25; 95% CI: 1.32 – 8.00). Though they reported lower levels of recreational exposure (OR, 0.50; 95% CI: 0.21 - 1.19). Additionally, Siskind, Whiteman, Aitken, Martin, & Green (2005) found that individuals with melanomas of the head and neck were less likely to report sunburn history than individuals with melanomas of the trunk (OR, 0.48; 95% CI: 0.29 – 0.80). The Whiteman et al. and Siskind et al. studies provide evidence in support of an intermittent sun exposure hypothesis.

Trends in Incidence Rates of Melanoma by Anatomic Site

When trying to understand exposure patterns, it is helpful to review trends in incidence rates by anatomic sites, as they are not uniform (Dal et al. 2007; Houghton, Flannery, & Viola, 1980). In Sweden, Denmark, Connecticut, it was found that there was a rise in the overall melanoma incidence rate, however it was attributable to sites other than the head (the chronically most exposed site). In fact, the incidence rates for the head were the most age-dependent, similar to exposure patterns consistent with SCC (Dal et al., 2007; Houghton et al., 1980).

Moan & Dahlback (1992) studied the doubling rates of (age-adjusted) incidence of melanoma, and found that in men the doubling time for the head and neck was 2.5 that of the trunk. Similar differences between the sites were found for women too, though not quite as high (1.7). The doubling rates for women were the same for the lower extremities and for the trunk, suggesting similar types of exposure for those sites. Where as for men, the doubling rate of the lower extremities was 1.5 times that of the trunk (Moan & Dahlback 1992), suggesting that leg hair may have a protective effect for men (Osterlind et al., 1988). Likewise, in a review, Marks (2000) noted that there had been a fall in incidence rates for the head and neck, and an increase in incidence rates for the trunk (greater in males than females) and an increase on the lower limbs (females only). Considering the relationship between trends in incidence rates and gender, age, and changing behavior patterns over the past several decades, it has been surmised that they may give clues to the etiology of melanoma.

Sunlight Exposure and Anatomic Site

The most common sites for melanoma are on the trunk (back, chest, and shoulders) in men and on the lower limbs in women (Bulliard et al., 1997; Whiteman & Green, 1999). However, because the surface area of skin varies by anatomic site, it can be misleading to only report absolute numbers of melanoma tumors. Pearl & Scott (1986) developed the Relative Tumor Density (RTD) calculation in order to create a standard way of comparing melanomas between data sets for varying anatomic sites. For example, if one looks at the absolute

incidence rates of melanomas on the face compared to the trunk, the trunk usually has higher rates. However, when amount of surface area of the skin is taken into account, the incidence rates for the face are higher compared to the trunk (Bulliard et al., 1997; Elwood & Gallagher, 1998).

Age and Gender

Elwood & Gallagher (1998) examined the incidence of melanoma by age and anatomic site. Specifically, they found that RTDs for the back, chest, and upper arm are higher than the face and ears up to age 50, and after 50 the trend reverses, suggesting a cumulative effect of sun exposure, or conversely an age associated decrease in capacity to repair DNA (Goukassian et al., 2000; Wei, Matanoski, Farmer, Hedayati, & Grossman, 1993).

Bulliard (2000) also examined the relationship of melanoma to anatomic site by gender and age. Though, age was included as a continuous variable, yielding more information than age as a dichotomous variable. For sites likely to be chronically exposed, such as the ears, scalp, and neck, the incidence rate for men rises dramatically compared to that of women, beginning around the late 40s for ears and the late 50s for the scalp and neck. This pattern may be associated with the lack of protection men receive from hair styles. Furthermore, the incidence rates for men and women for melanomas of the scalp and neck do not peak and drop, instead they continue to rise (Bulliard, 2000; Osterlind et al., 1988), suggesting that melanomas on those sites arise from cumulative exposure overtime, with more accumulation for men than women due to hair style.

Whereas for intermittently exposed sites such as the trunk and the lower limbs, the incidence rates for men and women separate at much younger ages, specifically in the early 30s for the trunk and as young as the teens for the lower limbs (Bulliard, 2000). Moreover, the incidence of melanoma of the trunk rises steeply for men and women until around age 50 - 60 and 35 - 40, respectively and then level off or fall, as opposed to continuing to increase (Bulliard, 2000; Osterlind et al., 1988). Based on the data from his study, (age of divergence between sexes and the type of curve, i.e. continual increase or a falling off) Bulliard purports that incidence of melanoma at certain anatomic sites can be considered a substitute indicator for pattern of UV exposure.

Latitude

The latitude gradient for the incidence of malignant melanoma is estimated at an increase of 5% per degree of latitude closer to the equator (Bulliard, Cox, & Elwood, 1994). However, similar to age and gender, the relationship of incidence of melanoma with latitude is not completely uniform across anatomic sites, ranging from an increase per degree of 3.38% to 6.29% for males and 0.49% to 6.24% for females (Bulliard, 2000). The male trunk and the female scalp & neck were shown to have the highest increase with latitude at 6.29% and 6.24% respectively.

The relationship between latitude and incidence of melanoma also varies by race or ethnicity. Hu et al. (2004) found a negative correlation between the incidence of melanoma and latitude of residency for blacks, Hispanics, and

whites, though it was only significant for black males (r=-0.80, p=0.05). Though, Eide & Weinstock (2005) found a significant negative correlation between latitude and the incidence of melanoma in whites (r=-0.85, p<0.001).

Rationale for Thesis Research

Although much epidemiologic data exists regarding UV radiation and the incidence of malignant melanoma, exposure-response relationships based on the incidence of melanoma and UV radiation by pattern of exposure have not yet been developed. In this study, exposure-response relationships will be defined for two patterns of sun exposure, chronic and intermittent, using certain anatomic sites as proxies for pattern of exposure. We hypothesize that the slope for intermittently exposed sites will have a larger positive slope relative to chronically exposed sites. This hypothesis is based on the report of Bulliard (2000) that presented New Zealand incidence rates for teens and young adults showing a steep rise in melanoma on the trunk, an intermittently exposed site compared to chronically exposed sites on the ears, other face, and scalp & neck. Exposure-response relationships are also examined for each anatomic site by gender.

The public health objectives of this analysis include improving our understanding of risk of malignant melanoma by anatomic site, gender, and geographic location. The findings of this analysis may allow improvement of health education messages to focus on the most pertinent behavior changes necessary to reduce the risk of malignant melanoma. The exposure-response relationships will also likely help to predict future disease burden. This

information can be used to inform primary care physicians and dermatologists about opportunities to adapt skin cancer screening practices for men and women, and in particular geographic areas. Additionally, as concern about the reduction of ozone in the stratosphere continues, updated exposure-response relationships can help to quantify possible implications from ozone loss.

Specific Aims

This thesis assesses the exposure-response relationship of malignant melanoma incidence and solar UV radiation at various anatomic sites, by gender, and by geographic location in the United States. Our specific aims are to:

1) Evaluate various measures of solar ultraviolet (UV) radiation exposure including ground-level and satellite monitoring and modeling estimates, and select an appropriate measure to use in an ecologic analysis of national cancer registry data.
2) Assemble data from the Surveillance, Epidemiology, and End Results (SEER) Program on the age-adjusted incidence of malignant melanoma by anatomic site and geographic location.
3) Using linear regression, develop exposure-response models for anatomic sites stratified by gender. Using a mixed effects model, evaluate the strength of the association for chronically exposed and intermittently exposed anatomic sites by gender.

Main Hypothesis

Linear regression models of the incidence of malignant melanoma on solar ultraviolet radiation will have larger positive slopes for intermittently exposed anatomic sites relative to exposure-response models for chronically exposed anatomic sites.

Chapter 2 – Methods

Measures of Solar UV Exposure (Specific Aim 1)

An evaluation was performed of several data sources of various measures of ultraviolet (UV) radiation exposure using the following criteria: representativeness to environmental levels, SEER site registry location cross match, data structure, and ability to download data. The data sources of UV radiation include the National Weather Service under the National Oceanic Atmospheric Administration (NOAA/NWS) sites, the Environmental Protection Agency (EPA) UV-Net Program sites, and the United States Department of Agriculture (USDA) sites. The purpose of developing a UV Index under NOAA/NWS and in collaboration with the EPA, was to give the public information about risks from sun exposure and aid in their ability to protect themselves from sun-related health problems later in life (www.epa.gov). The EPA UV-Net Program is designed to provide information on the geographical distribution and temporal trends of UV radiation in the United States. In addition, the data is used by scientists who study the effects of UV on plants, animals, and other materials (www.epa.gov). The USDA developed a monitoring and research network of surface UVB radiation measurements in part to inform the agricultural community about potential damaging effects of UVB to agricultural crops and forests (http://uvb.nrel.colostate.edu).

NOAA/NWS has developed a UV Index (www.cpc.ncep.noaa.gov) that is calculated using a radiative transfer model, forecasted ozone data, forecasted

cloud amounts, and the elevation of the forecast cities. The radiative transfer model incorporates the erythema action spectrum which accounts for the fact that human skin responds differently to each wavelength of radiation. The weighting function, specifically the McKinlay-Diffey Erythema action spectrum, is used to calculate an erythema dose rate (Scotto et al., 1996). The radiative transfer model also incorporates the time of day, day of year, and latitude to determine the UV irradiances. Cloud conditions are incorporated into the UV Index using the following transmission proportions; 100% for clear skies, 89% for scattered clouds, 73% for broken clouds, and 32% for overcast clouds. The UV Index is adjusted at an increase of 6% per kilometer for elevation of the forecasted city. Currently, the UV Index does not incorporate three potentially important factors, variable surface reflection, atmospheric pollutants, or haze. Without atmospheric pollutants and haze included, the UV Index is overestimated. Alternatively, not incorporating the surface reflection most likely underestimates the UV Index (www.cpc.ncep.noaa.gov).

Surface observations of UV radiation are collected by the EPA UV-Net Program and the USDA. The EPA UV-Net Program uses mainly Brewer Spectrophotometers to obtain UV radiation measurements. These measurements are then weighted using the McKinlay-Diffey Erythema action spectrum, however it assumes clear sky conditions, and elevation and ozone are not incorporated into the data. The USDA sites use a variety of instruments to collect UV irradiances, including the UV-MFRSR, VIS-MFRST, Yankee Broadband sensor, and UVB-1 Broadband Pyranometer. Using surface

measurements of solar UV radiation to predict UV irradiances invites error through variances in measuring instruments as well as errors in data collected during time periods when instruments are not calibrated (Weatherhead et al. 1997).

The NOAA/NWS UV Index is calculated for 58 cities across the United States and the EPA UV-Net Program observes UV irradiances at seven urban sites and fourteen National Park sites across the United States. There are 39 USDA sites located across the United States. Table 1 presents a cross tabulation of NOAA/NWS, EPA UV-Net Program & USDA sites with the SEER Cancer Registry sites. As can be observed, the SEER sites all have a corresponding site to the NOAA/NWS sites, however the match with the EPA UV-Net Program sites is incomplete by three cancer registry sites from 1973 and three more from 2000. The match with the USDA sites is also incomplete by two cancer registry sites from 1973 and two from 2000.

Examining data structure, the NOAA/NWS UV Index data is available by monthly averages beginning in 1995 and going through 2005. The EPA UV-Net Program data is available daily from mid-1998 to 2003, and the USDA data is available varying for different cities from 1993 to 2007. The NOAA/NWS data structure is conducive to easy data collection. The daily UV Index data for each year from 1995 to 2005 is available easily by accessing a folder on this website, ftp://ftp.cpc.ncep.noaa.gov/long/uv/cities/ . The EPA UV-Net Program data structure is much more cumbersome. The UV irradiances are weighted though they are not integrated over the UVB spectrum. There are approximately 30

scans per day and the data files are not in a text format that can be easily converted into a spreadsheet file. Similarly, the USDA data is also cumbersome. A UV scan is done every three minutes every day from 3pm to 1am, for about 200 scans per day. This data is stored in a text format. However, the USDA UV irradiances are weighted and they are also integrated over the UVB spectrum.

In a comparison of the UV Index and UV irradiances as measured by Brewer Spectrophotometers, Fioletov, Kerr, McArthur, Wardle, & Mathews (2003) found that UV irradiances derived from each of these methods agreed within 2-3%. Lemus-Deschamps, Gies, Rikus, Strong, & Dixon (2004) found an agreement within 1 UV Index unit of which the main difference was due to cloud conditions.

Assessing the three UV data sources based on the original criteria; general agreement with surface measurements, the manner in which the NOAA/NWS UV Index is calculated, its coverage of all SEER cancer registry sties, the data structure, and the ability to download the data, the NOAA/NWS UV radiation data source was selected for the UV exposure data. UV Index data will be compiled using three metrics, average annual cumulative UV Index (AAC UVI), and the number of days at or above UV Index 7 (High Zone) and UV Index 10 (Very High). The High and Very High Zones were chosen because the number of minutes to skin damage for both of these zones is ten minutes or less.

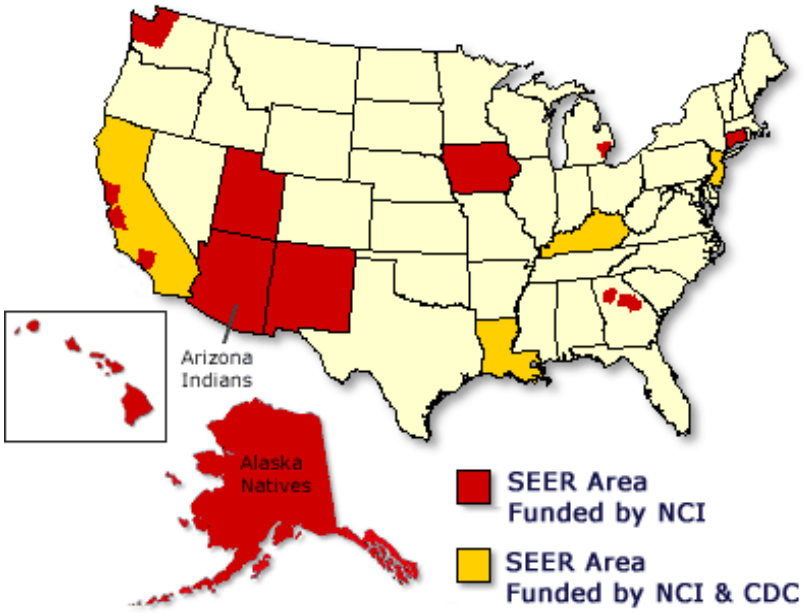
Table 1: SEER Registries by UV Measurement Locations

Latitude	SEER Sites			NOAA/NWS Sites		EPA UV-Net Program Sites		USDA Sites	
	Year Started	State	City/Region	State	City/Region	State	City/Region	State	Station Name (closest town)
37.8	1973	California	San Francisco-Oakland	California	San Francisco	California	Sequoia NP (115 miles SE of San Jose)	California	UC Davis Climate Station (Davis)
34.1	1992	California	Los Angeles	California	Los Angeles	California	Riverside (30-40 miles E of LA)	California	Desert Research & Extension Center (Holtville - SE of LA)
37.3	1992	California	San Jose-Monterey	California	San Francisco	California	Sequoia NP (115 miles SE of San Jose)	California	UC Davis Climate Station (Davis)
41.8	1973	Connecticut		Connecticut	Hartford				
33.8	1975	Georgia	Atlanta	Georgia	Atlanta	Georgia	Atlanta	Georgia	Bledsoe Research Farm (Griffin - 30 miles S of Atlanta)
33.5	1992	Georgia	Rural Georgia	Georgia	Atlanta	Georgia	Atlanta	Georgia	Bledsoe Research Farm (Griffin - 30 miles S of Atlanta)
41.6	1973	Iowa		Iowa	Des Moines				
38.3	2000	Kentucky		Kentucky	Louisville				
30.0	2000	Louisiana		Louisiana	New Orleans			Louisiana	LSU Central Research Station (Baton Rouge)
42.3	1973	Michigan	Detroit	Michigan	Detroit			Michigan	University of Michigan Biological Station at Douglas Lake (Pellston)
39.4	2000	New Jersey		New Jersey	Atlantic City				
35.1	1973	New Mexico		New Mexico	Albuquerque	New Mexico	Albuquerque	New Mexico	Jornada Experimental Range (Las Cruces)
40.8	1973	Utah		Utah	Salt Lake City	Utah	Canyonlands NP (185 miles SE of SLC)	Utah	Utah Climate Center (Logan)
47.6	1974	Washington	Seattle-PS	Washington	Seattle	Washington	Olympic NP (40-80 miles NE of Seattle)	Washington	Albion Field Station (Pullman)

Assembly of Malignant Melanoma Data (Specific Aim 2)

The next step was to assemble incidence rates of malignant melanoma by anatomic site using SEER data. There are 18 SEER registries encompassing approximately 26 percent of the US population (see Figure 1). A few studies have been performed assessing the completeness of SEER data. Comparing the SEER registry to the National Program of Cancer Registries (NPCR), Wingo et al. (2003) found that NPCR rates were lower than SEER rates for melanoma. Zippin, Lum, & Hankey (1995) found a crude estimated completeness of reporting in 1987 for six participating SEER areas to be 97.7% with a registry-caseload standardized rate of 96.8%. Alternatively and melanoma specific, Clegg, Feuer, Midthune, Fay, & Hankey (2002) found that the initial-incidence-case-counts accounted for only 88% of the estimated final counts for the incidence of melanoma. Clegg et al. emphasized the importance of using a reporting adjustment, because the difference between reporting-adjusted and unadjusted incidence rates for melanoma in 1998 was 14% in whites. Noting that it would take an additional estimated 17 years to reach 99% of melanoma cases to be reported from the actual diagnosis year.

Figure 1: SEER Registries



A data use agreement was signed with the SEER program in July 2007 and a database was created using SEER*Stat (Version 6.3.5) using data from the years 2000 to 2004. The Alaskan Native Tumor Registry and the Arizona Native American Registry were excluded, due to the population being restricted to the high-risk white race. The Greater California Registry was also be excluded due to the wide range in latitudes within this designated geographic area. Additionally, the Hawaiian Registry was excluded because the exposure in this equatorial location is very different from the contiguous 48 states and more than 50% of the UV data is missing for Hawaii.

The analysis data set was restricted to include invasive melanoma (not in situ), and exclude acral lentiginous melanomas (ALM) and lentigo maligna melanomas (LMM). ALM was excluded because it is very rarely found in the population of study, and LMM was excluded because it mainly affects older populations (Chang, Karnell, & Menck, 1998).

The database includes anatomic site designations including, lips (C44.0), eyelid (C44.1), ear (C44.2), face (C44.3), scalp & neck (C44.4), trunk (C44.5), arm & shoulder (C44.6), and leg & hip (C44.7) (www.seer.cancer.gov). The face, eyelid, lip, ear, and scalp & neck were considered sub-sites of the head. The head, arm & shoulder, trunk, and the leg & hip were considered the four main anatomic sites. The incidence of melanoma for the head was considered to be a chronically exposed anatomic site. The arm & shoulder and leg & hip are not included in the intermittent exposure categorization because of the potential for mixed exposure for these anatomic sites is high, where as the trunk has a very low likelihood of mixed exposure. Likewise, the trunk alone will be considered the intermittently exposed anatomic site. The demographic variables include age and gender. As previously described, the analysis was restricted to the white race.

Statistical Analysis

In this analysis, the independent variables are the UV metrics and the dependent variables are the incidence rates of malignant melanoma. A simple linear regression (SLR) analysis was performed for each anatomic site by gender and for the two types of exposure, intermittent and chronic. The linear regression method was selected because the variables, AAC UVI and age-adjusted incidence of melanoma (cases of melanoma per 100,000), are continuous.

Surface area adjusted (SAA) incidence rates were calculated using the following conversions: head - 8.9% total body surface area; arm & shoulder –

16.5%; trunk – 24.5%; and leg & hip – 47.5% (Ellwood & Gallagher, 1998). A mixed effects model (MEM) using SAA incidence rates was used to test the hypothesis that the slope of the regression line for intermittently exposed anatomic sites is positive and steeper than the slope of the regression line for chronically exposed anatomic sites (Specific Aim 3). In addition, interaction effects between anatomic site and gender were explored.

The MEM, as opposed to a General Linear Model was chosen to accommodate hierarchical structure induced by the registry locations. The MEM incorporates fixed effects, such as AAC UVI, pattern of exposure, or gender, as well as random effects or clustering factors, such as SEER registry location, i.e. geographic location. Specifically, instead of the analysis treating the anatomic site incidence rates within a various geographic location as independent, this model can accommodate potential correlations among them due to being clustered at their geographic location, i.e. registry location. The SEER registry location is added as a random effect because each cancer rate is nested within a site. A specific incidence rate by anatomic site within one SEER registry can then be correlated with other incidence rates at the same SEER registry (Pinheiro & Bates, 2000).

Chapter 3 – Results

The fourteen SEER Cancer Registries ranged in latitude from 30.0 – 47.6 degrees north (Louisiana State to Seattle, Washington). Three UV metrics were used in the analysis of the data (Table 2): (1) Annual Cumulative UV Index (AAC UVI), (2) the number of days from 1995 – 2005 at or above UV Index 7 (UVI-7), and (3) the number of days from 1995 – 2005 at or above UV Index 10 (UVI-10). Graphic representations of the AAC UVI and UVI-7 can be found in Figures 2 and 3, respectively.

Table 2: UV Metrics

SEER Cancer Registry	Latitude	Average Annual Cumulative UV Index	Number of Days from 1995 - 2005	
			UV Index $\geq$ 7	UV Index $\geq$ 10
Louisiana State	30.0	2062.9	1567	63
Rural Georgia	33.5	1806.6	1148	23
Atlanta, Georgia	33.8	1806.6	1148	23
Los Angeles, California	34.1	2010.0	1525	90
New Mexico State	35.1	2158.8	1722	355
San Jose, California	37.3	1760.8	1197	44
San Francisco, California	37.8	1760.8	1197	44
Kentucky State	38.3	1479.5	683	2
New Jersey State	39.4	1378.8	495	0
Utah State	40.8	1637.3	1072	40
Iowa State	41.6	1326.0	500	1
Connecticut State	41.8	1221.9	280	0
Detroit, Michigan	42.3	1205.3	323	0
Seattle, Washington	47.6	961.9	95	0

Figure 2: Average Annual Cumulative UV Index (AAC UVI) by Latitude

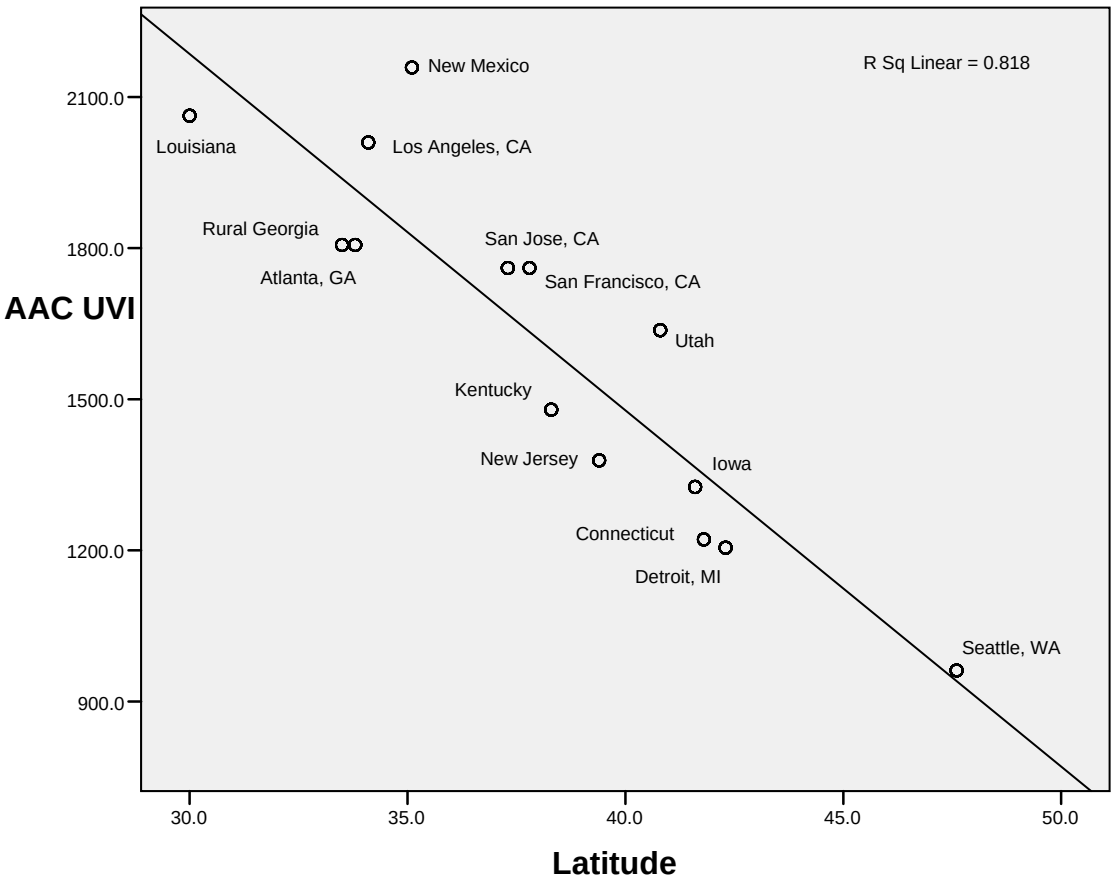
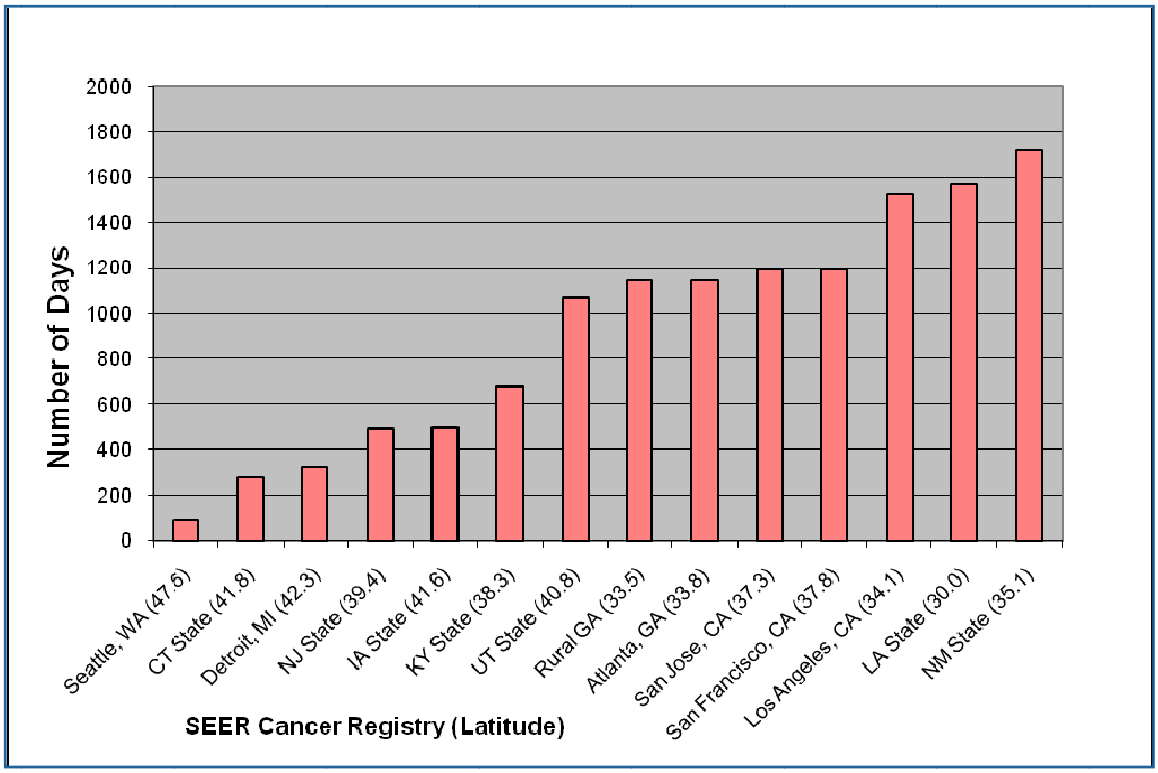


Figure 3: Number of Days from 1995 – 2005 at or above UV Index 7



The AAC UVI in New Mexico State and Utah State are slightly higher than their counterparts at similar latitudes (Figure 2), which is largely attributable to the higher elevations of these states. Even so, a strong linear relationship is observed between ACC UVI and latitude ($R^2 = 0.818$) (Figure 2). Similarly, Figure 3 shows that the total number of days from 1995 – 2005 at or above UV Index 7 does not increase uniformly with decreasing latitude; this may be attributable to differences in elevation and cloud cover.

The incidence rate of malignant melanoma in whites in all seventeen of the SEER registries of individuals 75 or younger is 21.0 per 100,000 people (Table 3). The rate for males (24.9) is about 30% higher than that of females

(17.7). The rates for males and females within the fourteen SEER registries used in this analysis were very similar (24.1 – males, 17.4 – females). Table 4 lists the rates of malignant melanoma by gender for each of the fourteen SEER Cancer Registries used in the analysis.

Table 3: Incidence of malignant melanoma in whites in SEER registries (2000 – 2004, ≤ 75 years)

# of Registries	Parameter	Male	Female	Male & Female
Seventeen	Count (%)	33,268 (57.1)	24,990 (42.9)	58,258 (100)
	Rate / 100,000	24.9	17.7	21.0
Fourteen	Count (%)	23,815 (56.6)	18,261 (43.4)	42,076 (100)
	Rate / 100,000	24.1	17.4	20.5

Table 4: Incidence of malignant melanoma in whites by SEER registry (2000 – 2004, ≤ 75 years)

SEER Cancer Registry	Male Rate / 100,000	Female Rate / 100,000	Male & Female Rate / 100,000
Louisiana State	17.0	11.5	14.1
Rural Georgia	24.9	18.5	21.6
Atlanta, Georgia	35.2	24.6	29.4
Los Angeles, California	22.4	13.5	17.6
New Mexico State	22.2	16.1	18.9
San Jose, California	23.3	15.9	19.4
San Francisco, California	26.0	15.9	20.8
Kentucky State	22.5	17.4	19.7
New Jersey State	25.2	17.7	21.1
Utah State	26.0	19.8	22.7
Iowa State	17.7	15.9	16.6
Connecticut State	25.9	19.9	22.6
Detroit, Michigan	25.4	19.7	22.2
Seattle, Washington	29.4	24.7	26.8

Table 5 presents the incidence rates of the anatomic sites reported in the SEER registries. The head is a combination of the following sub-sites, face, eyelid, lip, ear and scalp & neck. Table 6 also presents incidence rates by gender. For all anatomic sites, except for the leg & hip, the male rate is higher than the female rate.

Table 5: Incidence Rates of Malignant Melanoma in whites by Anatomic Site (from 14 SEER Registries, 2000 – 2004, ≤ 75 years)

Anatomic Site	Rate / 100,000
Head	3.73
Arm & Shoulder	4.64
Trunk	6.91
Leg & Hip	4.00
Face	1.63
Eyelid	0.13
Lip	0.05
Ear	0.50
Scalp & Neck	1.42

Examining AAC UVI by the incidence rates of melanoma (genders combined and genders separated), the Simple Linear Regression (SLR) showed an inverse relationship (see Figures 4 and 5). The SLR analyses produced three intercepts that were significantly different from zero; however the slopes approached statistical significance (from zero) for both genders combined (p=0.051, β_1 = -1.217).and for males (p=0.063, β_1 = -1.525), but not for females (p=0.107, β_1 = -0.909).

Table 6: Incidence Rates of Malignant Melanoma in whites by Anatomic Site & Gender (from 14 SEER Registries, 2000 – 2004, ≤ 75 years)

Incidence Rates of Malignant Melanoma		
Anatomic Site	Mean Rate / 100,000 (Range)	
	Male	Female
Head	5.45 (4.13 - 8.49)	2.21 (1.77 - 3.06)
Arm & Shoulder	5.14 (3.50 - 7.89)	4.26 (2.73 - 6.40)
Trunk	9.15 (5.52 - 13.50)	4.93 (3.17 - 7.50)
Leg & Hip	2.61 (1.37 - 3.76)	5.38 (3.06 - 8.32)
Face	2.17 (1.62 - 3.15)	1.16 (0.66 - 1.56)
Eyelid	0.14 (0.00 - 0.25)	0.12 (0.00 - 0.20)
Lip	0.06 (0.02 - 0.39)	0.03 (0.00 - 0.06)
Ear	0.90 (0.69 - 1.40)	0.15 (0.00 - 0.25)
Scalp & Neck	2.16 (1.52 - 3.69)	0.75 (0.60 - 2.31)

Figure 4: Incidence Rate of Malignant Melanoma

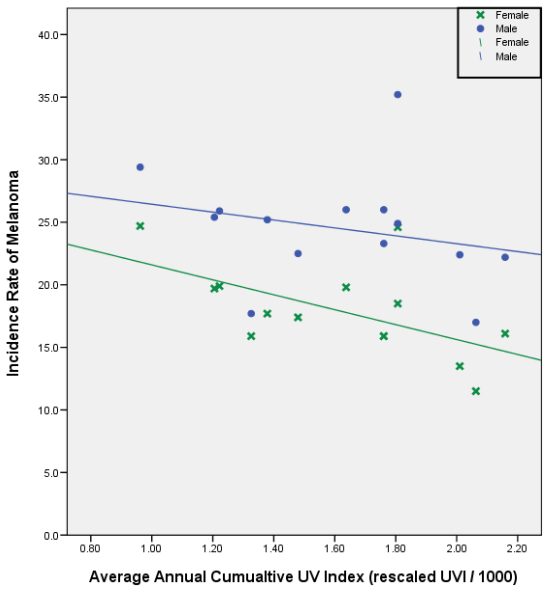
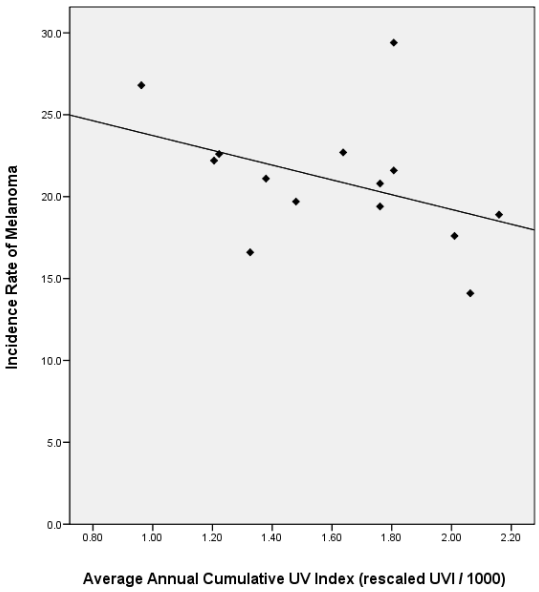


Figure 5: Incidence Rate of Malignant Melanoma by Gender



SLR analysis was performed using the anatomic sites, head, arm & shoulder, trunk, and leg & hip by gender on AAC UVI, UVI-7, and UVI-10. Diagnostics tests were completed to test error terms for constancy of variance and normality, and to check for linearity of the regression function and outliers. The regression parameters for the four anatomic sites on AAC UVI and UVI-7 were acceptable. Additionally, the correlation between AAC UVI and UVI-7 was almost perfect ($R^2 = 0.984$), therefore no further reporting of the exposure-response relationships between melanoma and UVI-7 are presented. The regression parameters for the UV metric, UVI-10, were questionable. More importantly almost 30% of the exposure sites did not have any occurrences of UV Index over 10 in the eleven year period. Therefore UVI-10 was not used in any further analyses.

The SLR analyses for AAC UVI produced intercepts that were significantly different from zero for each of the main anatomic sites and for both men and women (see Figures 6 – 9). In addition, slopes were significantly different from zero for the male and female trunk (males p=0.043, $\beta_1 = -3.284$; females p=0.025, $\beta_1 = -2.195$. The slope for female leg & hip was also significant (p= 0.007, $\beta_1 = -2.549$).

Mixed-effects model (MEM) analysis indicated that slopes of males and females were different from each other for the four main anatomic sites. However, the leg & hip was the only site with a significant interaction term between gender and AAC UVI, $F(1, 15) = 11.00$, $p = 0.005$, representing a difference between the intercepts of males and females.

Figure 6: Incidence Rate of Malignant Melanoma of the Head

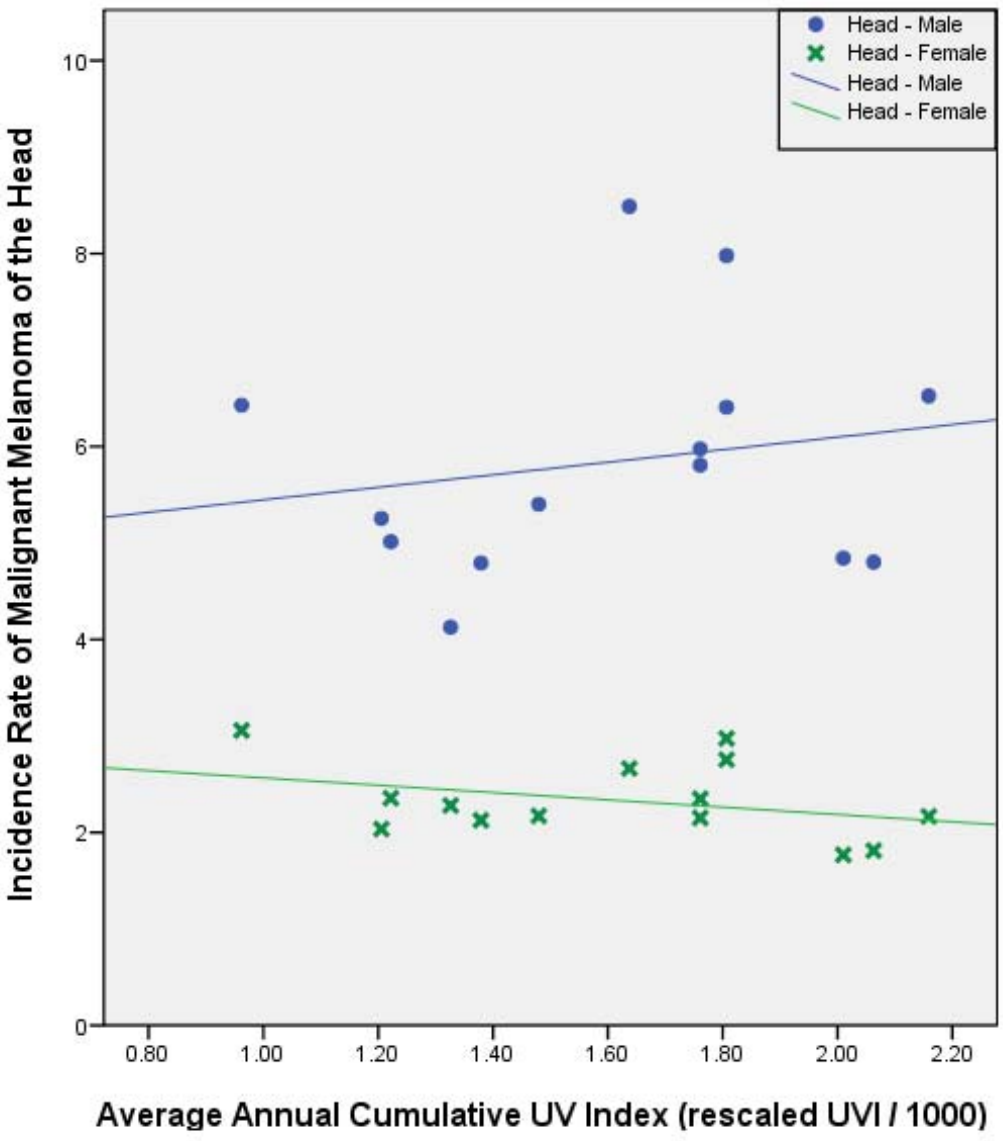


Figure 7: Incidence of Malignant Melanoma of the Arm & Shoulder

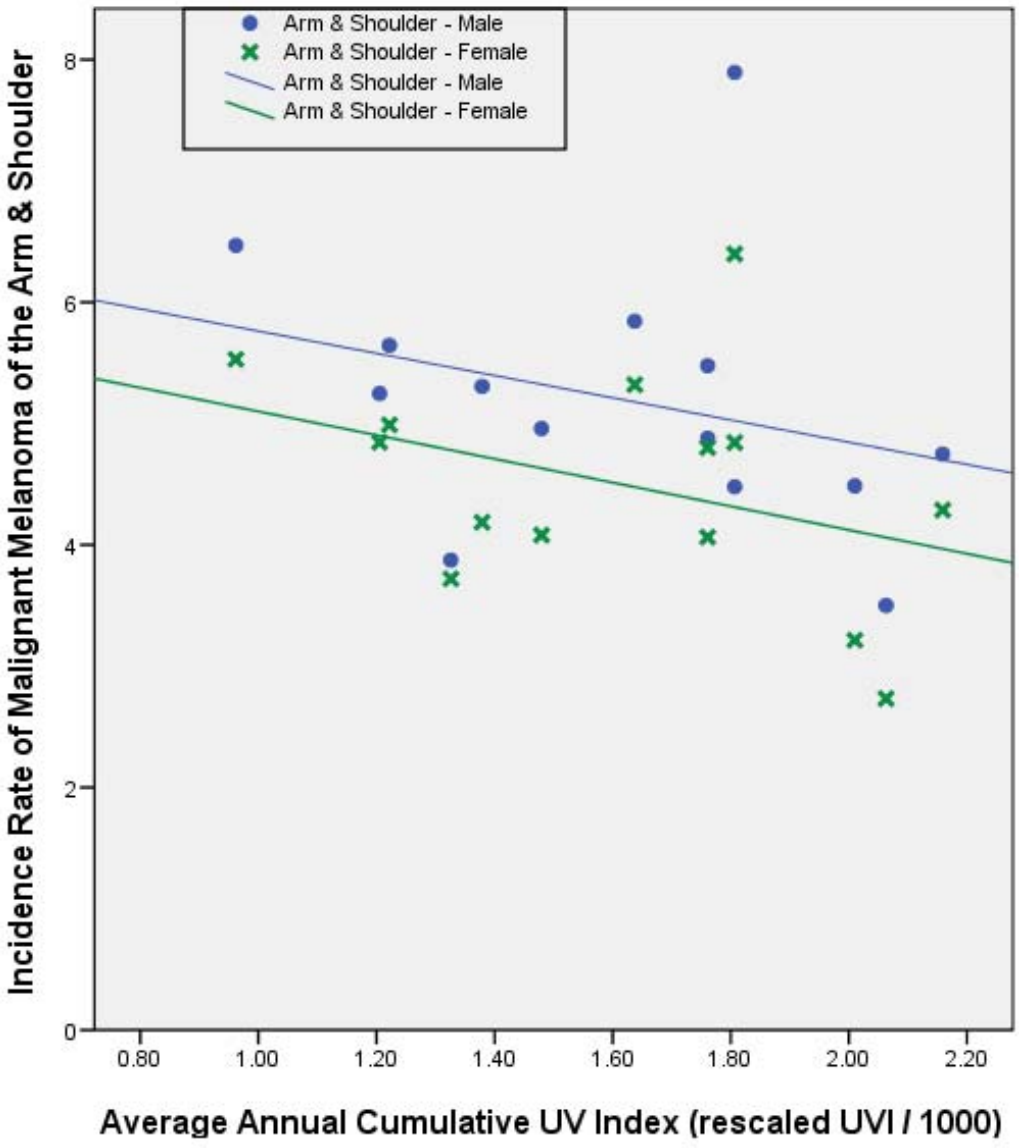


Figure 8: Incidence Rate of Malignant Melanoma of the Trunk

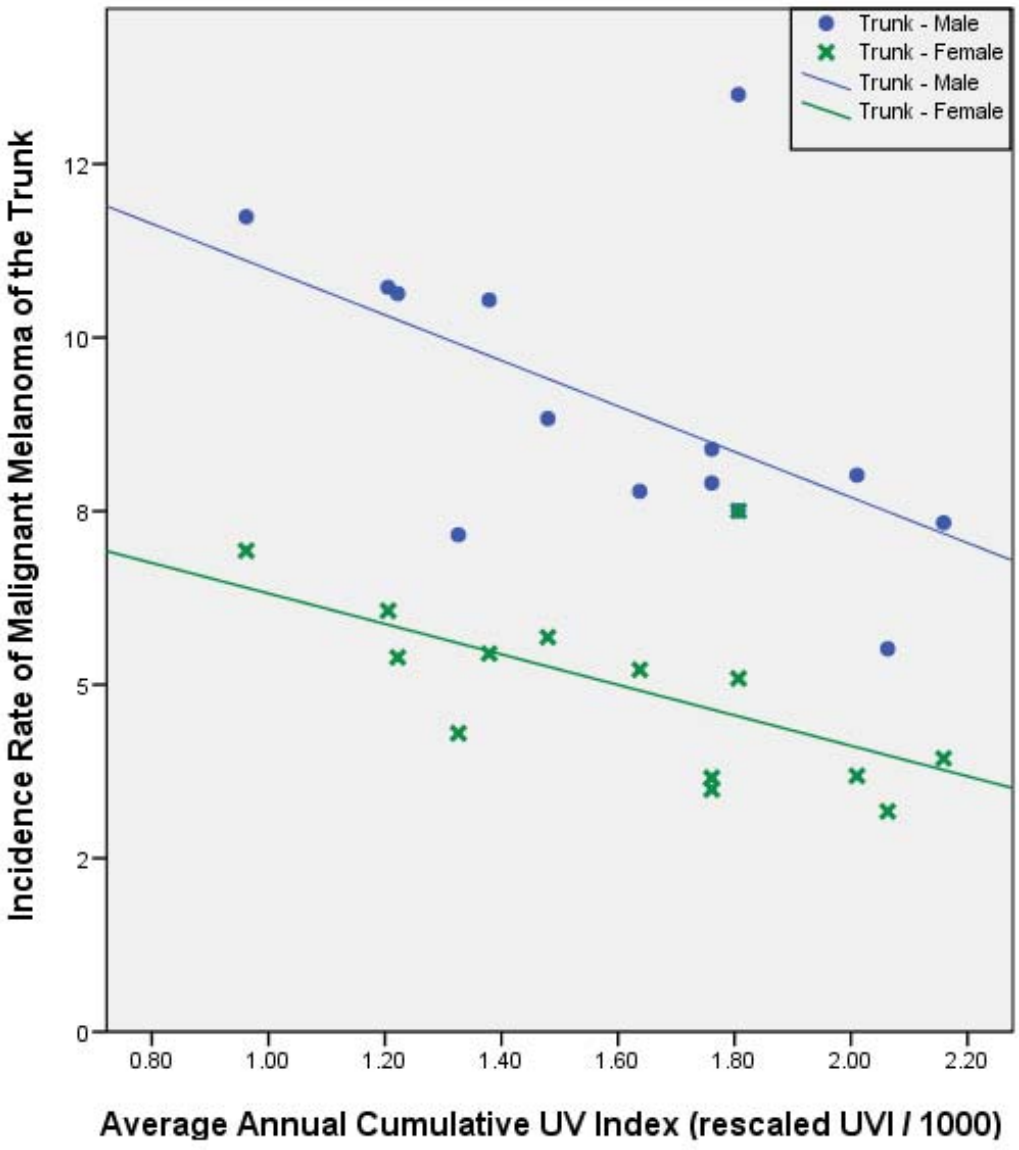
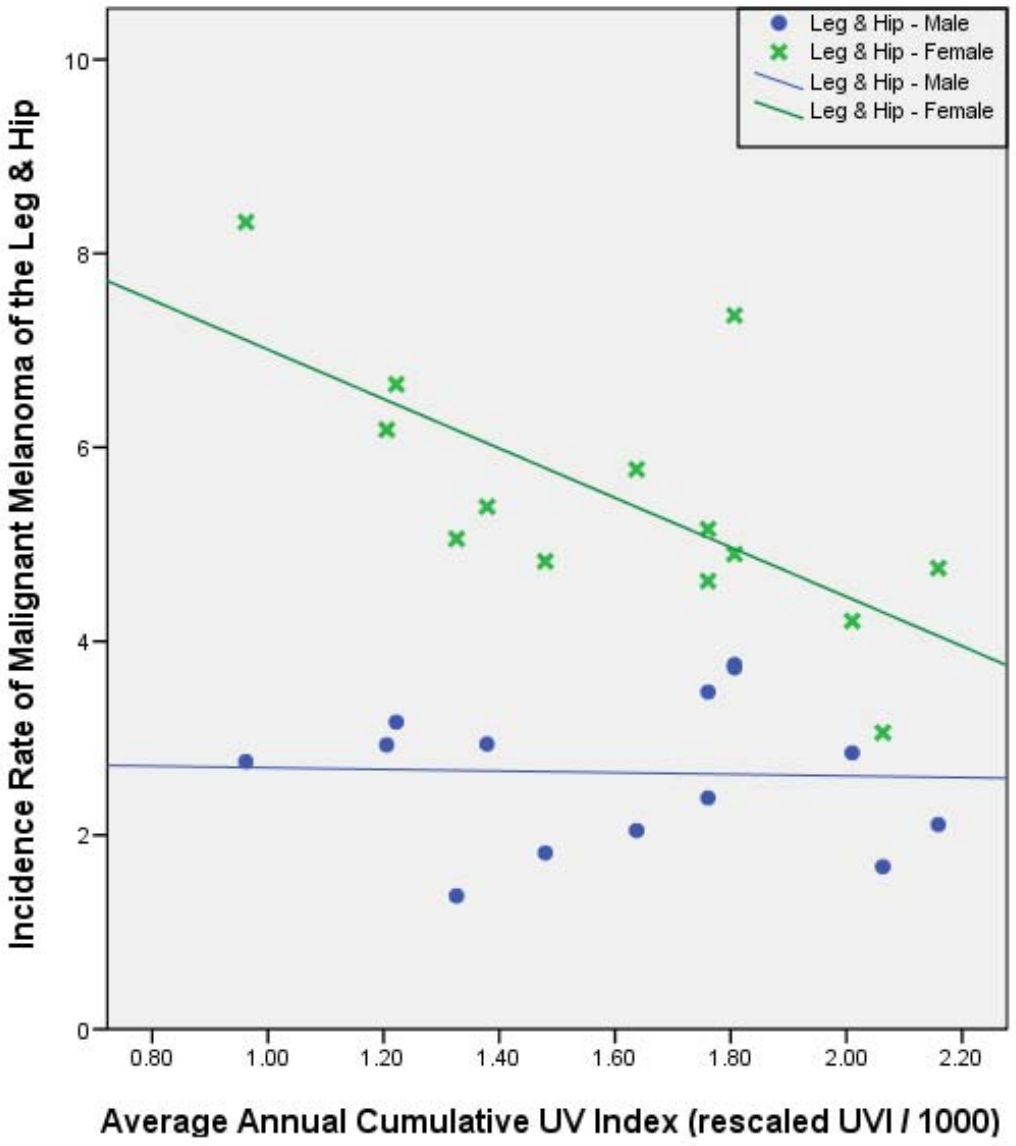


Figure 9: Incidence of Malignant Melanoma of the Leg & Hip



Regarding the five sub-sites of the head, the SLR analysis for AAC UVI indicated that intercepts were significantly different from zero for the male and female face, male and female ear, and the female eyelid (see Figures 10 – 14). In addition, the slope was significantly different from zero for the female eyelid

(p=0.041, β_1 = -0.090). The MEM analysis indicated that slopes of males and females were different from each other for all of the sub-sites, except for the eyelid. However, a significant interaction term was reported for the eyelid (F (1, 17) = 4.78, p = 0.043), representing a difference between the intercepts of males and females.

Figure 10: Incidence of Malignant Melanoma of the Face

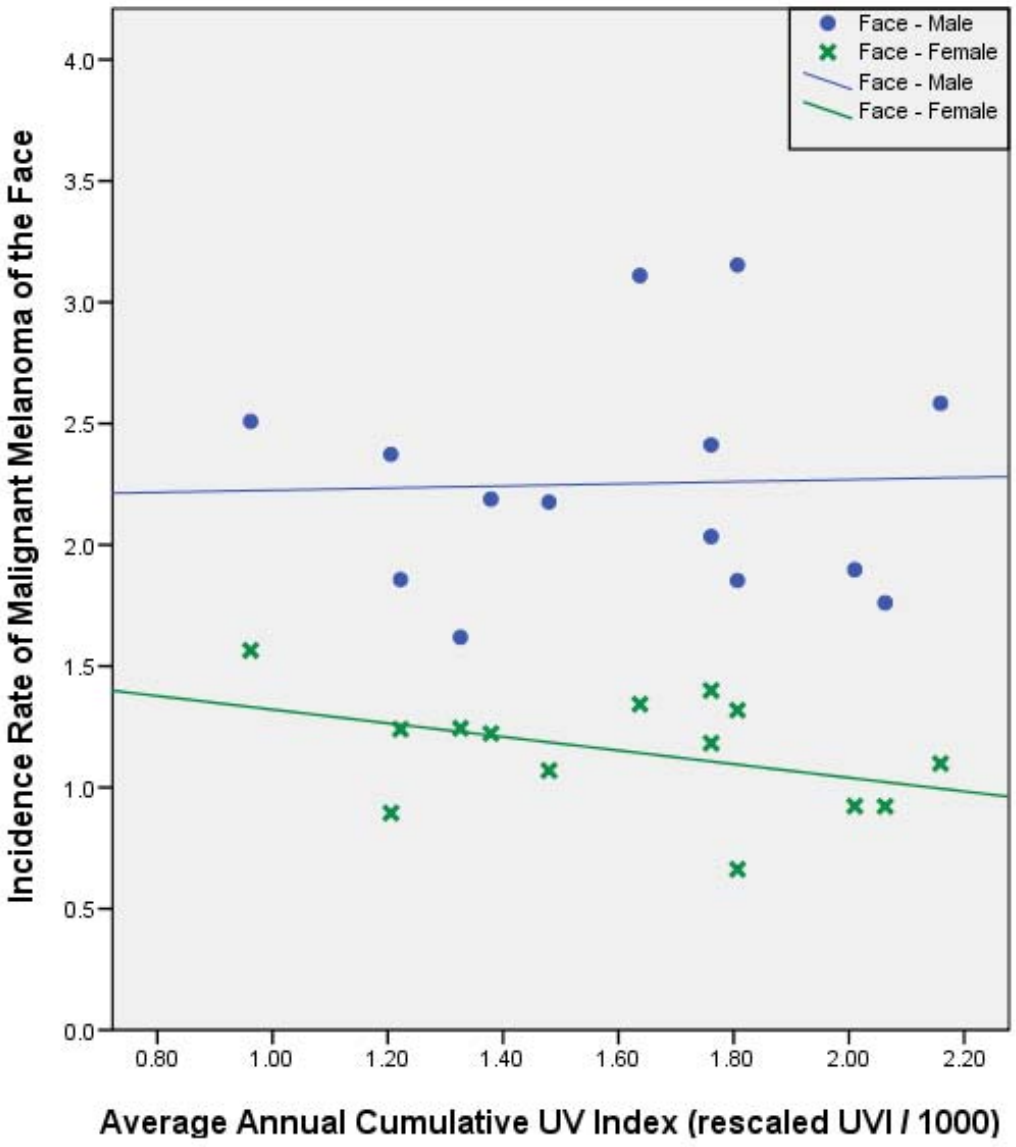


Figure 11: Incidence of Malignant Melanoma of the Eyelid

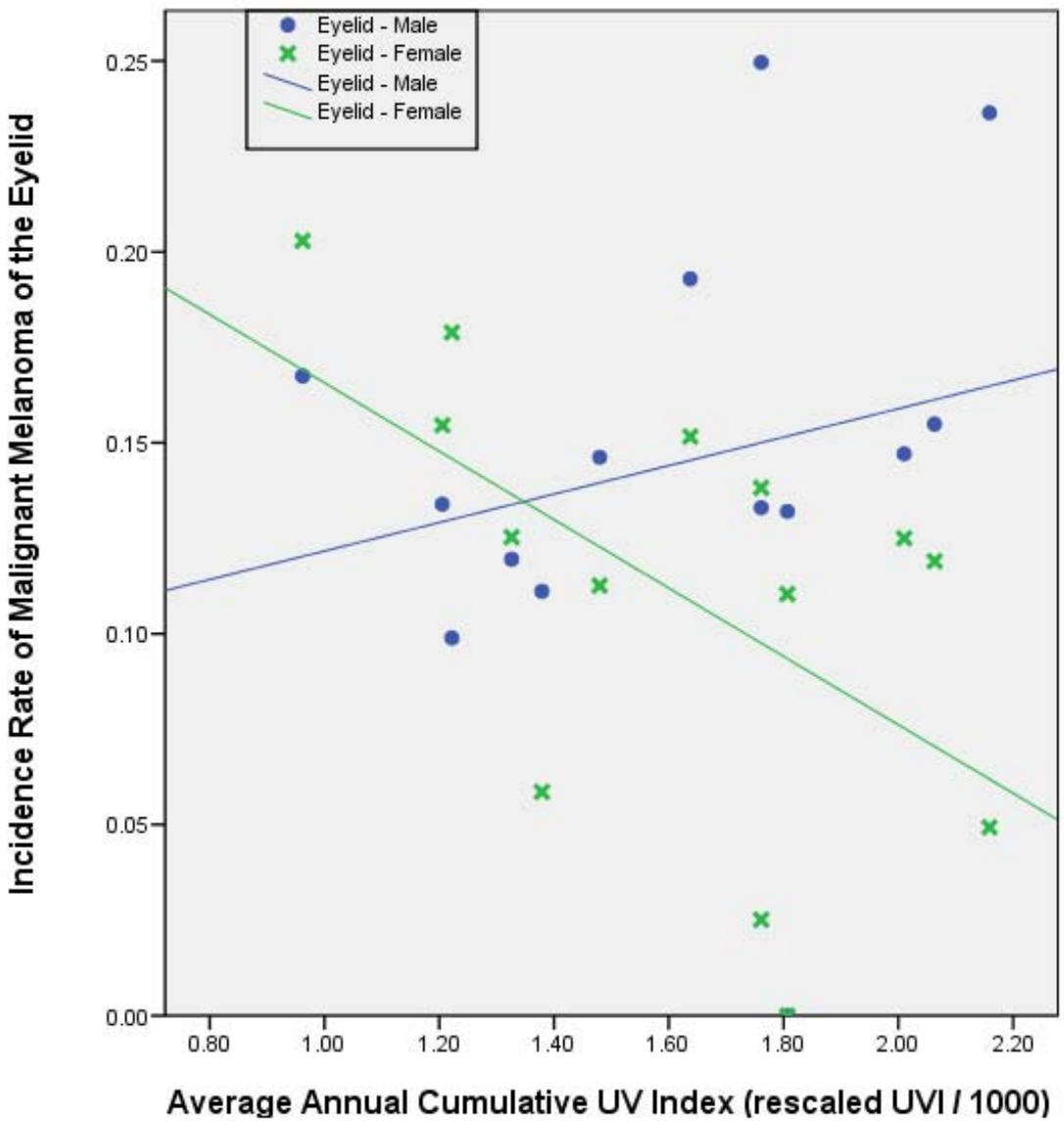


Figure 12: Incidence of Malignant Melanoma of the Lip

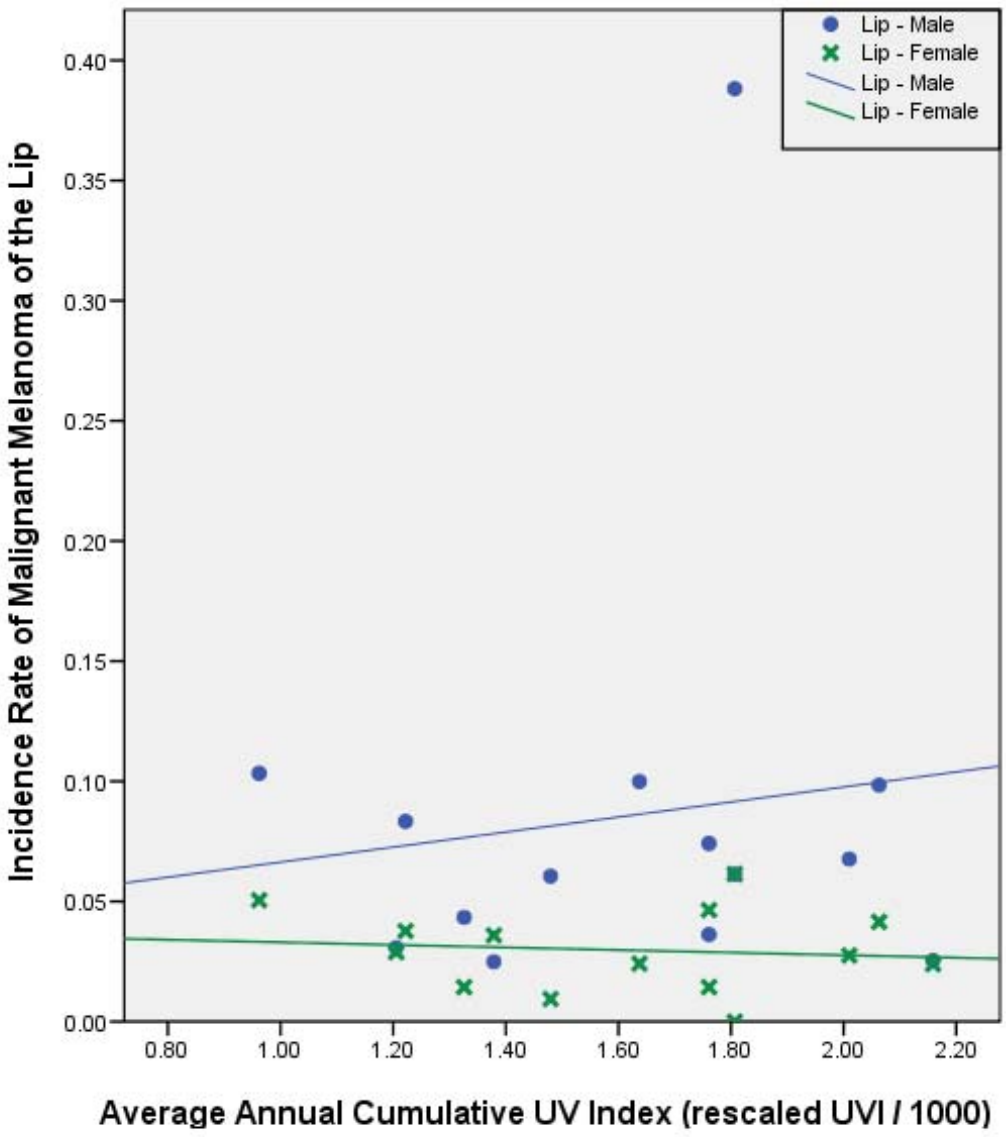


Figure 13: Incidence of Malignant Melanoma of the Ear

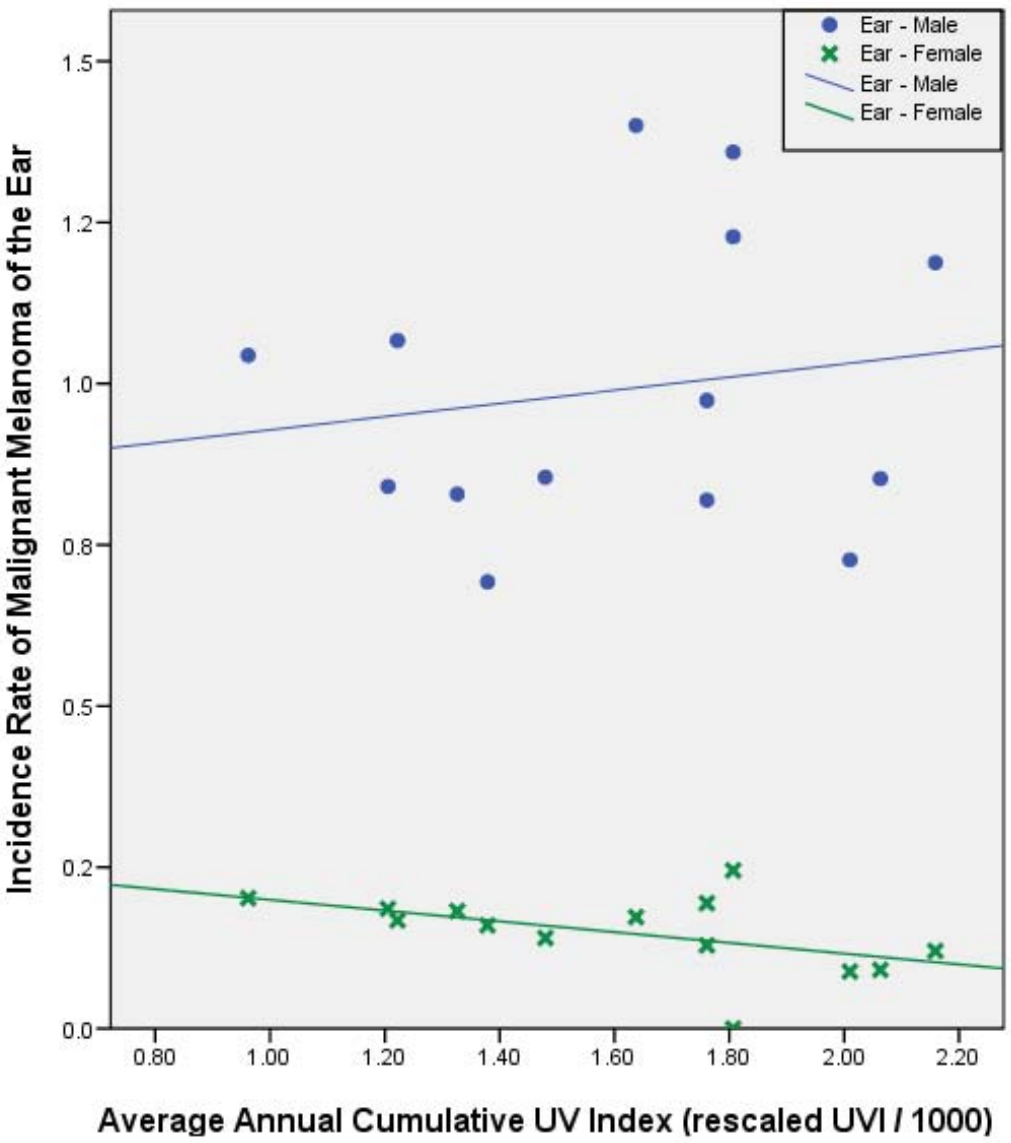


Figure 14: Incidence Rate of Malignant Melanoma of the Scalp & Neck

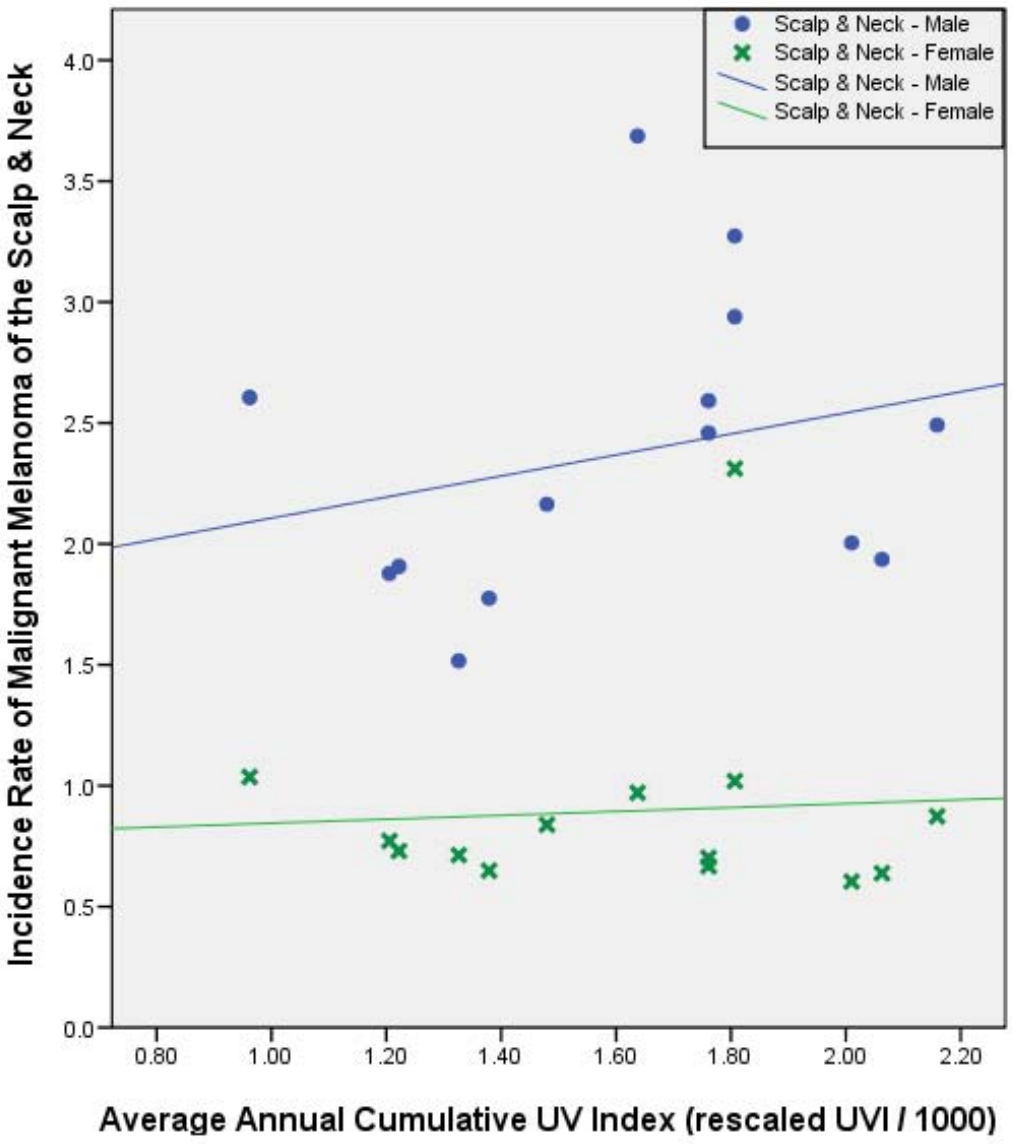
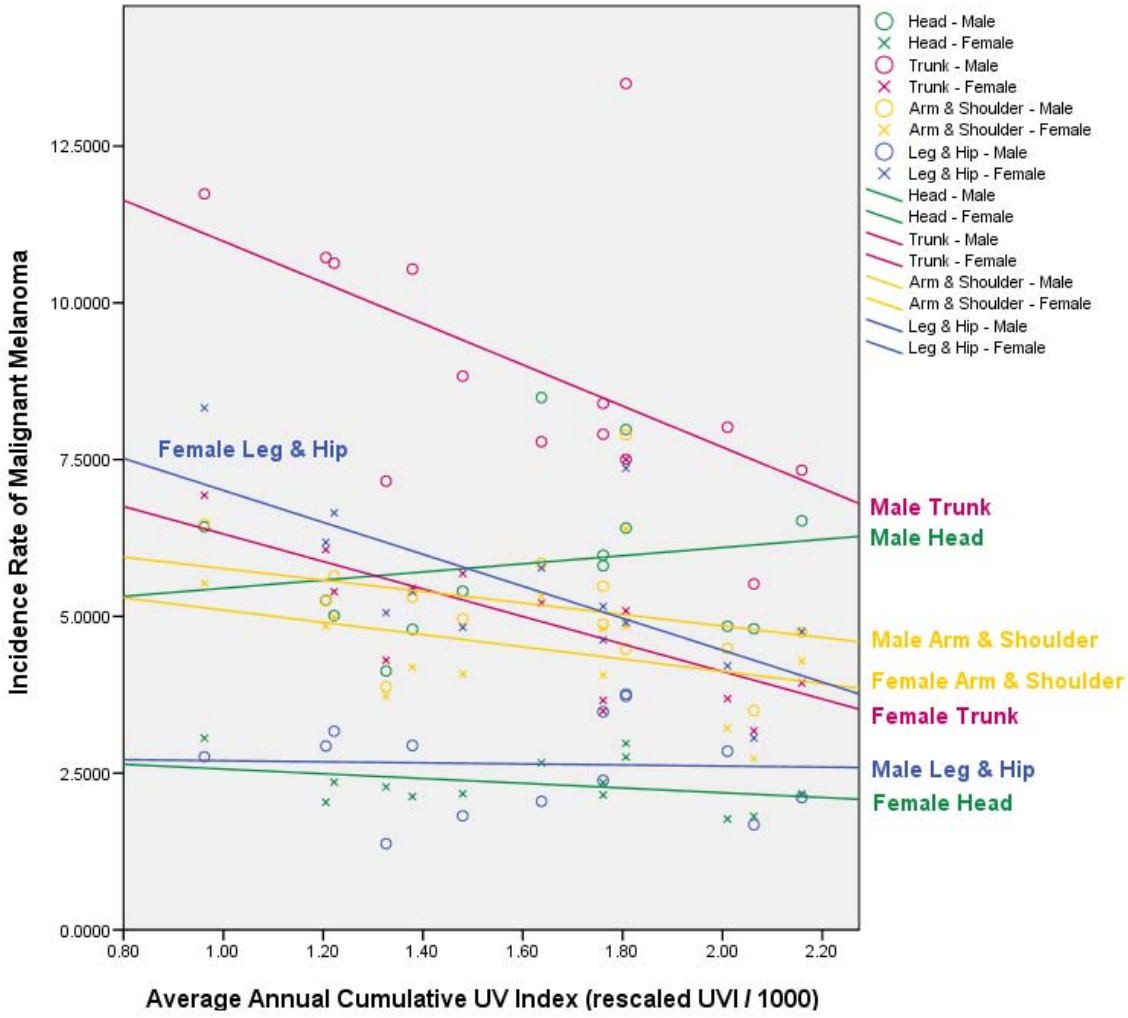


Figure 15: Regression Lines for the Four Main Anatomic Sites by Gender for Incidence Rates on AAC UVI



When comparing the regression lines of the incidence rates of the main anatomic sites by gender on AAC UVI (Figure 15), the male trunk and female trunk have relatively high incidence rates, and both have strong negative slopes when regressed on AAC UVI. Regression lines for male and female arm & shoulder are also negative. Female leg & hip, but not male leg & hip, display a strong negative relationship. The incidence of male head tumors increases with

increasing AAC UVI, but the female head exposure-response relationship is slightly negative in slope.

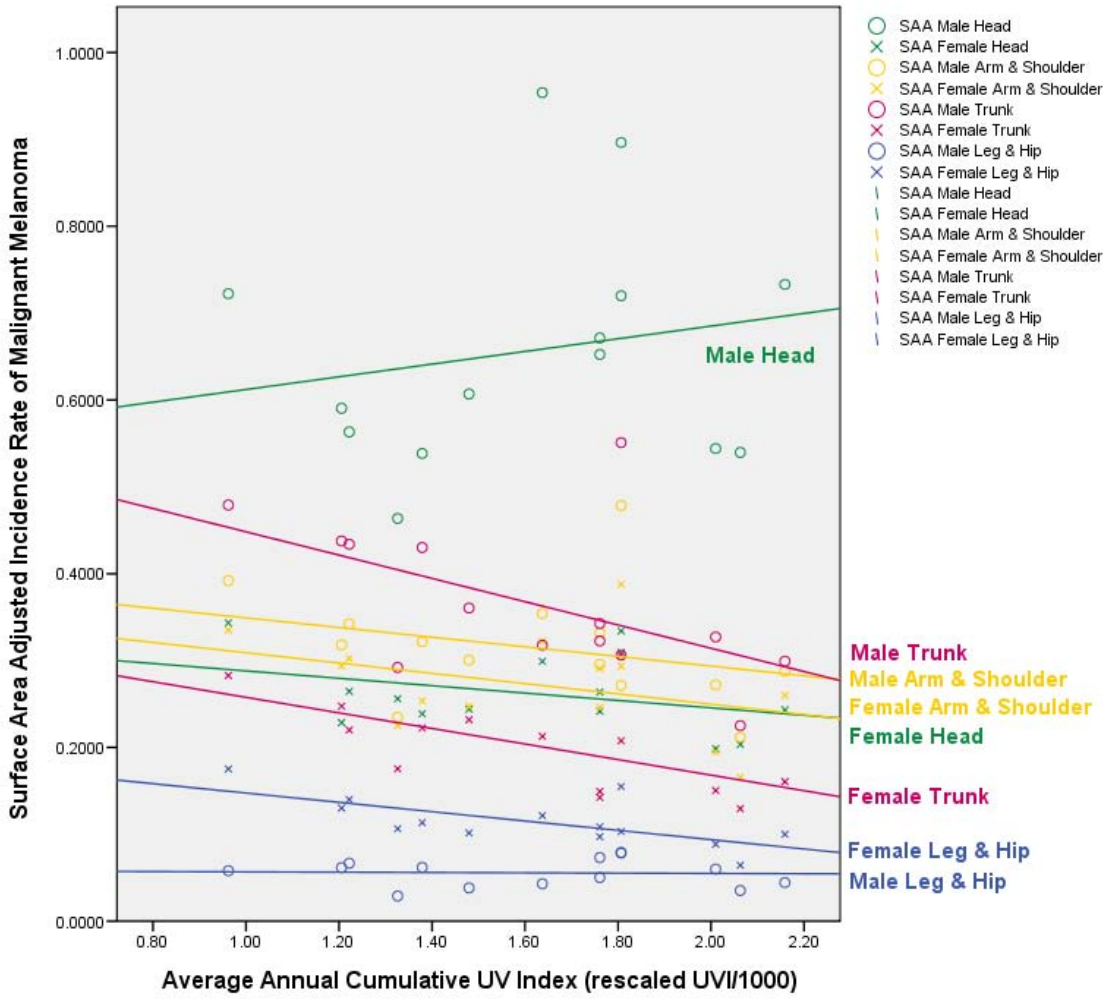
The malignant melanoma (MM) incidence rates adjusted for skin surface area are presented in Table 7, as well as the male-to-female ratios. The ear, for males and females, has the highest SAA incidence rates, as well as the highest male-to-female ratio.

Table 7: Surface Area Adjusted Incidence Rates of Malignant Melanoma

SAA Incidence Rates of Malignant Melanoma			Male / Female Ratio
Anatomic Site	Mean Rate / 100,000 (Range)		
	Male	Female	
Head	0.61	0.25	2.44
Arm & Shoulder	0.31	0.26	1.19
Trunk	0.37	0.20	1.85
Leg & Hip	0.05	0.11	0.45
Scalp & Neck	0.35	0.12	2.92
Ear	1.80	0.30	6.00
Face	Proportion of Surface Area Not Available		1.87
Eyelid			1.23
Lip			2.00

Figure 16 presents exposure-response regression lines for the four major anatomic sites, adjusting for skin surface area. Male head has the highest incidence rate. The SAA incidence rate for male trunk is still relatively high; however the incidence rate for female leg & hip after adjustment for skin surface area is reduced considerably.

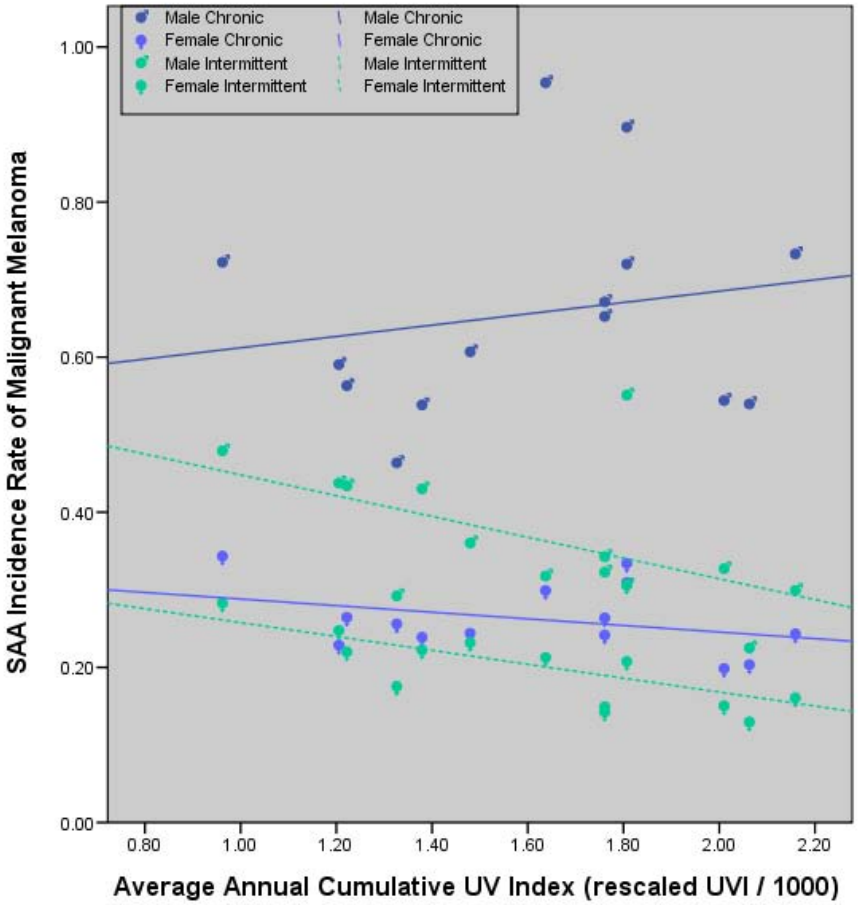
Figure 16: Regression Lines for the Four Main Anatomic Sites by Gender for Surface Area Adjusted Incidence Rates on AAC UVI



In an effort to develop a model that best predicts the relationship between AAC UVI and the SAA incidence rates of melanoma, MEMs were run with the independent and dependent variables, plus gender, anatomic site, and all possible interactions. The model that best fit included AAC UVI ($F(1, 11) = 2.24$, $p = 0.164$), gender ($F(1, 93) = 233.11$, $p < 0.001$), anatomic site ($F(3, 93) = 201.17$, $p < 0.001$), and the interaction term, gender*anatomic site ($F(3, 93) = 56.51$, $p < 0.001$).

To test the hypothesis that the slope for the exposure-response relationship of incidence rates of intermittently exposed anatomic sites (trunk) on ACC UVI is positive and steeper relative to chronically exposed anatomic sites (head), a MEM was used. The slope for the intermittently exposed anatomic sites was not steeper than the chronically exposed sites (Figure 17), therefore the null hypothesis was not rejected. However, the MEM indicated that the slopes were significantly different when controlling for gender ($p < 0.001$, $\beta 1 = -0.175$, $F(1, 43) = 44.00$, $p < 0.001$). When an interaction term between gender and exposure was introduced into the model, it was not significant.

Figure 17: Regression Lines for SAA Incidence Rates for Intermittently and Chronically Exposed Anatomic on AAC UVI



Chapter 4 – Discussion

While we failed to reject the null hypothesis regarding differences in malignant melanoma incidence at intermittently exposed anatomic sites in males and females compared to chronically exposed anatomic sites, our analysis revealed an unanticipated trend in the exposure-response relationship. The incidence of malignant melanoma (MM) for typically unexposed areas of the skin is higher in locations with lower UV exposure. Interestingly, Lee (1997) predicted that the melanoma death rates in the US would be geographically neutral or begin an inverse relationship by the early 21st century, and Jemal, Devesa, Fears, & Hartge (2000) found that the north-south gradient of melanoma mortality decreased from the periods 1950-1959 to 1985-1994. Our analysis of US incidence rates may be the first to observe this reversal.

It is important to emphasize that our findings do not provide contradictory evidence of the causal relationship of solar UV exposure and malignant melanoma risk. Rather, our analysis sheds some light on other possible determinants of MM risk that are playing a larger role now than during the first half of the 20th century. We hypothesize that public health prevention messages, the availability and use of sunscreen, sun avoidant behavior, and social & psychological influences may be operating to reduce the incidence of MM in southern latitudes. Our exposure-response relationships suggest that these prevention factors have been more effective in areas with high solar UV levels relative to more northern US locations.

Unfortunately, there is a paucity of rigorous research on the effectiveness of skin cancer prevention programs. In a systematic review by Saraiya et al. (2004) sufficient evidence was only found for educational and policy interventions in primary schools and programs for adults in outdoor recreational or tourism settings. Other prevention programs such as, educational and policy interventions in child care centers and in secondary schools and colleges, programs in outdoor occupational settings, healthcare system and provider settings, mass media campaigns, programs for caregivers (parents), and multi-component community-wide programs have not been sufficiently evaluated and it is not possible to judge their effectiveness at this time. Opportunities to increase the rigor of research regarding skin cancer prevention efforts include measuring key sun protective behaviors and health outcomes, controlling for confounders, describing key demographic variables, stronger descriptions of UV exposure, more thorough descriptions of interventions used, and use of longer follow-up periods (Saraiya et al., 2004).

Documentation of public health interventions for sun protection and skin cancer prevention in the US is also lacking in the medical literature. Inclusion of UV Index in mass media weather reports began routinely in 1994 (Geller et al., 1997). In 1995, Geller et al. found that 91% and 68% of the cities they surveyed broadcast the UV Index on television on a weekly and daily basis. The geographic location of the cities where these announcements occurred was not reported, although we believe it is reasonable to assume that these announcements occurred in higher exposure areas. We posit that if public health

prevention messages were aired more frequently in the “Sun Belt”, sunscreen use and sun avoidant behavior may have increased.

There is also a lack of published data on the implementation of public health campaigns to reduce over exposure to the sun and skin cancer incidence and mortality in the US. The “Slip, Slop, Slap” campaign was used by the American Cancer Society in New Mexico and Arizona in the mid-1990’s on billboards, print media, and via public service announcements on radio and television (William Lambert, personal communication, May 12, 2008). Over the last ten years, the U.S. EPA has conducted its “Sunwise” campaign in U.S. schools (www.epa.gov/sunwise/). News coverage is another important influence on public awareness. In their analysis of newspaper coverage in the two decades, Stryker, Solky, and Emmons (2005) demonstrated that the number of newspaper articles were low prior to 1986, and remained relatively constant from the mid-80s to the present. The content areas of prevention and detection received much less attention, 32% and 24% of all stories, relative to treatment at 47%. Overall, skin cancer prevention education has not received consistent or high profile attention in the U.S.

Additionally, and possibly more of an influence than protecting oneself from the far off possibility of developing skin cancer in later life, is the desire to avoid the immediate pain associated with sun burns. This behavioral tendency, may be more prevalent in Sun Belt latitudes where high exposures may occur throughout the year, relative to northern latitudes. Importantly, the results of this study allude to the vital nature of protecting oneself on a daily basis, year round,

despite living in northern latitudes. Opportunities for burning exposures in northern latitudes during non-summer months include skiing, winter vacations in sunny climates, and “sun seeking” on clear days in the spring and fall seasons. Potentially, people living in northern latitudes may use tanning booths throughout the year, which would increase their risk for MM (Swerdlow & Weinstock, 1998).

Psychological influences may also play a role in the northern and southern differences observed in our analysis. Tanned skin is viewed as more attractive, healthy, and athletic (Lamanna, 2004; Vail-Smith & Felts, 1993). Speculatively, northerners may take more chances with the sun, in the hopes of ‘getting some color’, and the fear of not knowing when they will be exposed to the sun again. Persons living in northern latitudes may risk exposures without protection to the point of becoming burnt, because ‘some color’ is viewed and valued as more attractive or healthy than is ‘no color’.

The anatomic sites that showed a statistically significant inverse relationship between incidence rates of melanoma and UV exposure were the male and female trunk and female leg & hip, demonstrating a possible association with parts of the body that are valued as attractive by both men and women and therefore more likely to be neglected from sun protective behaviors.

The male head demonstrated a positive relationship with UV exposure. The very nature of chronic exposure, in that males expose their heads regularly to the sun and do not receive protection from longer hair, especially covering the ears and the scalp & neck, may contribute to the continued positive exposure-response relationship for the male head. Men typically do not wear cosmetics

and are probably less likely to wear face lotion with sun screening properties. Additionally, Miller et al. (1996) found that men were less likely than women to know what melanoma is, and Koh et al. (1991) found that women were more likely to attend melanoma/skin cancer screenings in Massachusetts than men.

The graphs of age-adjusted incidence rates by age-at-diagnosis (data not shown) for this study were similar to Bulliard's (2000) graphs for New Zealand residents. Our data showed the age at gender separation to occur later in life for chronically exposed anatomic sites (late 40s for the head), and for the intermittently exposed sites (early 40s for the trunk and mid teens for the leg & hip). The curves for chronically exposed anatomic sites also continued to rise, and the curves for intermittently exposed sites rose, then flattened or dropped off. Our findings were inconsistent with Bulliard's characterization of a positive exposure-response relationship between UV as measured by latitude and the incidence of melanoma at intermittently exposed anatomic sites. In contrast, our study showed a negative exposure-response relationship for intermittently exposed anatomic sites.

Limitations

Inherent in the design of this study is the possibility of the ecological fallacy; the relationships presented in this analysis are observed at a population level and therefore may not apply on an individual level (Portnov, Dubnov, & Barchana, 2007). The exposure data is applied using an overall index to large geographic areas, on a scale ranging from city to entire states, and the incidence

data is applied to populations in the SEER registry network on similar scales. However, this fallacy is unlikely, given the extensive case-control study literature establishing the relationship between sun exposure, sunburns, and malignant melanoma (Autier & Dore, 1998; Elwood & Jopson, 1997). A greater constraint on the interpretation of our analysis is the lack of data necessary to control for confounding (described below). Despite these limitations, we are of the opinion that the exposure-response relationships observed in this analysis at least represent the presence of a negative relationship that is worthy of further investigation.

The potential for exposure misclassification must also be acknowledged, although it is likely to be non-differential across the 14 SEER sites, and result in a bias towards the null. Therefore, the inverse exposure-response relationships that we observed can be interpreted as conservative. Other possible limitations of the exposure data include using the UV Index as a proxy for UV exposure; specifically the UV Index lacks the incorporation of surface reflection, including an inland/coastal gradient (Green & Siskind, 1983), atmospheric pollutants, and haze in the calculation. However, these factors may offset each other and ultimately not contribute a net bias in one direction.

Accompanying the potential bias associated with varying behavior patterns among the SEER registry locations is the potential for bias associated with geographic mobility or migration from one part of the country to another. 1990 Census data (www.census.gov) provides some insight on the size and direction of migration bias for the states of the 14 SEER registries used in this

analysis. (The 1990 Census was selected in view of the 10-15 year induction period for MM.). In Northern states with SEER registries, 3% are foreign born, whereas in the Southern states, 9% are foreign born. In Washington, the most northern state with a SEER registry, 52% of the population was born outside of the state, of which fourteen percent are from California, a high sun exposure state. Overall among the SEER registry states used in this analysis, when adjusting for population size, about twice the number of people have moved from the North to South, indicating a potential for differential misclassification of exposure. Though, the proportion of persons moving of white race was not ascertainable in these Census data. Furthermore, the estimates are aggregate numbers for entire states, not the more limited surveillance areas covered by some of the SEER registries. Individuals may have lived in several places in between their birth place and their residence at diagnosis of MM as well.

As previously mentioned, the greatest difficulty with ecologic studies stems from the lack of data necessary to control for confounding. The use of protective clothing and sunscreen, indoor-outdoor activity patterns, and the tendency for vacations in sunny locations is expected to vary by registry location. Additionally, in this analysis, the amount and frequency of public health education messages by geographic location was not controlled. Plausibly, skin cancer prevention messages could be associated with the exposure and the outcome, and the intensity of these prevention programs probably varies across the registry locations. Other potential confounding factors are present and probably vary by registry location. Although we restricted our analysis to persons of white

or Caucasian race, variation is expected in skin pigmentation, hair and eye color, freckling, ability to tan, propensity to burn, melanocyte proliferation, and nevi count. These factors likely vary by geographic locations, such as fair-skinned individuals of northern European heritage tending to live in the Midwest and northern latitudes.

Misclassification may also be present in the outcome data. While ascertainment of malignant melanoma by the SEER registries is very complete (> 95%), error may exist in the diagnosis of MM. A review by Helfand, Mahon, Eden, Frame, & Orleans (2001) reported levels of agreement between pathologists at 74% (kappa=0.61) for 140 paraffin slides of biopsied skin lesions in one study (Corona et al., 1996) and agreement of 62% (kappa=0.50) for 37 slides in another study (Farmer, Gonin, & Hanna, 1996), leading to the conclusion that histologic diagnosis of MM is difficult, and substantial opportunity for error exists. Data on variation in histologic accuracy by geographic locations in the US is not available, but accuracy could potentially vary between locations according to the incidence of MM and experience of pathologists.

Future Studies

This study has generated several new hypotheses regarding protective behaviors that may have played important roles in reversing the exposure-response relationship. First, it would be valuable to construct incidence trends for each of the SEER registry sites by anatomic site and gender from 1973 to the present. Comparisons for southern and northern locations could then be made. Next, it would be helpful to examine when the inverse relationship between UV

exposure and the incidence of malignant melanoma began. This could be estimated using incidence rates of SEER data at four-to-five year intervals beginning in 1973 and going through 2005, providing eight intervals for exposure-response relationships. Subsequently, a comprehensive timeline of skin cancer prevention activities in each of the SEER registry locations could be assembled and compared to incidence trends.

To better examine risk for MM at specific anatomic sites at the individual level, case-control study designs should be used. Case-control designs would be most efficient because of the long induction period of malignant melanoma. Controls would be matched by age, gender, race, and either have another cancer from the same registry system, or the same population that gave rise to the cases. Detailed information on past sun exposure could be collected, including: sun burn history, recreational patterns, occupational exposure, residential history. As well, data could be collected on protective behaviors such as sun screen use, sun avoidance, use protective clothing, awareness of public health prevention messages, and attitudes and beliefs regarding tanning, sun protection, and skin cancer.

To improve our ability to conduct secondary analysis of exposure-response relationships and incidence trends by anatomic site it would be helpful if there were more specific coding of anatomic sites. Specifically, coding the location of lesions on the extremities, for example, “arm & shoulder” should be coded into the following sub-sites: hand, forearm, upper arm/shoulder. Similarly, lesions on the “leg & hip” should be coded as occurring on the foot, lower leg,

thigh, hip, and buttock. This would allow for more specific evaluation of the risk levels for limbs, and allow more precise analysis of the risk of intermittent versus chronic sun exposure.

Public Health Implications

The public health implications of these findings include the necessity of improving public health education messages in northern latitudes. Specifically emphasizing the increased protection of the following anatomic sites with either sunscreen, protective clothing: male and female trunk, the male head, the male ear, and the female leg & hip, Shifting the paradigm from tanned skinned being viewed as attractive and healthy to one's natural skin tone being seen as beautiful is crucial in this effort (Weinstock, 2004). The psychological influences could be addressed with prevention education in high schools and on college campuses.

Regarding clinical applications, this information can also be used to educate primary care physicians and dermatologists about important additional screening practices tailored for individuals based on anatomic site and gender, as well as about the relationship between the incidence rate of malignant melanoma and geography, particularly the unanticipated higher rates in the northern latitudes. Clinicians should be just as suspicious of skin lesions on people in northern latitudes as they would be of people in southern locations. Regarding patient education, these results can serve as a reminder for clinicians to encourage their patients to use sunscreen or avoid sun during peak hours.

Finally, the male head is the only anatomic site with a substantial positive slope, i.e. a positive exposure-response relationship with UV. The male head also has the highest surface area adjusted incidence rate, with the majority of contributions from the ear, scalp, and neck. Specific additional daily protective actions, such as SPF 15 lotion and adorning hats to reduce UV exposure for these chronically exposed sites in men are warranted.

Conclusion

Our analysis demonstrated relatively reduced risk for malignant melanoma with residence in US locations with higher annual average cumulative UV Index values at most anatomic sites and for both men and women. Our prior assumption that malignant melanoma incidence rates are relatively higher in southern latitudes was not supported. Our analysis suggests that other factors may be offsetting higher regional UV levels. We posit that societal knowledge, attitudes, and beliefs about sun exposure and skin cancer may be shifting, particularly in locations where levels of solar UV radiation is more intense. Our findings also have implications for clinical practice in northern locations. It would be prudent to be as suspicious of skin lesions on a patient living in northern locations as in southern locations. Additionally, preventive education messages from clinicians or public health campaigns, informing individuals of northern locations of their risk for malignant melanoma, would be sensible.

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