META-ANALYSIS OF MELANOMA INCIDENCE IN THE UNITED STATES: DEMOGRAPHIC VARIATION AND RELATIONSHIP WITH UV INDEX AND LATITUDE

by
Charlie Pritchard

A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College.

Oxford
May 2014

Approved by

_____
Advisor: Dr. Carol Britson

_____
Reader: Dr. Clifford Ochs

_____
Reader: Dr. John Samonds

ABSTRACT

A link between exposure to ultraviolet (UV) radiation and melanoma skin cancer formation has generally been accepted in the scientific community, but precise quantification of such a link into a predictive equation is difficult to find in scientific literature. It was the aim of this study to determine if a quantifiable relationship exists between UV exposure and melanoma rates in the United States. Prior to the initiation of this study, it was hypothesized that existing predictive equations using accumulated UV index and latitude for general skin cancer incidence (i.e., including both melanoma and non-melanoma skin cancers) in Chile would be effective in predicting melanoma incidence rates in the United States. It was also hypothesized that melanoma rates for specific locations in the United States are related to the latitudes and accumulated UV index values for those locations, respectively. After accumulated UV index values, latitudes, and melanoma incidence rates for locations across the United States were obtained, regression analyses were performed in Microsoft Excel 2010® between accumulated UV index, latitude, and melanoma incidence rates for all demographic groups combined as well as differing demographic groups. The Chilean skin cancer equations (Rivas equations) were found to have no predictive power for melanoma rates in the United States. The only demographic group which had a significant relationship with accumulated UV index and latitude was American Indian or Alaska Native. For the remaining ethnicities, the regression analyses failed to reject the null hypotheses. Due to a variety of confounding variables and the limitations of the available data, a quantifiable relationship between UV exposure and melanoma might be determined only by more complex methodology. Factors such as skin color variation within each listed ethnicity,

differences in UV exposure patterns between individuals, and inconsistent reporting to cancer registries by dermatologists may preclude the formation of simple predictive equations for melanoma incidence. Future research which incorporates individuals' behaviors (e.g., time spent in the sun) may have more success.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

I would like to thank Dr. Britson for the valuable guidance she has provided me since freshman year, when, as a student in her Biology Recitation course I expressed to her my interest in skin. She instilled in me a fascination with histology through her excellent instruction in that course, and as a thesis advisor she was impeccable. I underwent several topic changes and complications over the last three years, but I learned and grew from the experience under her great tutelage. Her work in guiding my research and correcting my work has been invaluable. And I cannot express enough gratitude for the hours she spent meeting with me, even on weekends and holidays. I would also like to thank my second reader, Dr. Cliff Ochs, and my third reader, Dr. John Samonds, for their suggestions. Also, I extend my gratitude to Miguel Rivas of the University of Tarapaca in Chile for taking the time to respond to my questions concerning his paper. I also wish to thank the Department of Biology for supporting this thesis and for providing a high quality education over the past four years.

Furthermore, I thank the Honors College for all it has done to make my time at the University of Mississippi truly wonderful. The Honors College challenged me and helped me grow intellectually. It provided me with friendships I will cherish forever. Additionally, the Sally McDonnell Barksdale Scholarship allowed me to focus on my studies unclouded by the anxiety of financial burden. I also would like to thank Dr. Molly Pasco-Pranger and the Classics Department for kindling a love of all things Roman and for providing a balance to my science classes and thesis work. I am grateful for the constant support of my parents and friends. And I appreciate the technical advice given

by my sister Sarah and brother-in-law Chris for my earlier thesis idea. I am blessed to have been supported by so many wonderful people over the past few years.

INTRODUCTION

Melanoma is a cancer of the melanocytes and is the deadliest form of skin cancer. Melanocytes are specialized skin cells located in the epidermis which produce melanin, a pigment responsible for determining the color of human skin as well as protecting it from harmful ultraviolet rays (Hearing, 2011). Melanoma occurs when melanocytes proliferate uncontrollably, and may arise either from a pre-existing mole or with no apparent warning (American Academy of Dermatology, n.d.). According to Weir et al. (2011), melanoma often metastasizes (i.e., spreads to distant organs) and can prove to be lethal, but if caught early it has a very good prognosis. The authors did not specify what constitutes "early" nor did they include the precise prognosis at early stages. However, Weir et al. (2011) were likely referring to stage IA of the disease, in which the tumor is less than 1 mm thick and the 5-year survival rate is 97 percent (National Cancer Institute, "Stages of melanoma," n.d.; American Cancer Society, 2014).

In the United States, 921,780 people live with melanoma, and two percent of men and women will be diagnosed with the condition at some point in their lives (National Cancer Institute, "Surveillance, Epidemiology, and End Results (SEER) cancer statistics fact sheets," n.d.). It is estimated that 76,100 new melanomas will be diagnosed and 9,710 people will die from melanoma in the United States in 2014 (American Cancer Society, 2014). Melanoma is much less common than other skin cancers, accounting for less than two percent of all cases, but it causes the vast majority of skin cancer deaths (American Cancer Society, 2014).

Basal cell and squamous cell carcinomas are the two most common skin cancers, accounting for 3.5 million skin cancers in 2.2 million Americans each year, with the

majority of these being basal cell carcinomas (American Cancer Society, 2014). They are cancers of the keratinocytes, which are keratin-producing cells that make up the predominant cell type in the epidermis (Eckert and Rorke, 1989). Unlike melanoma, which spreads and metastasizes fairly rapidly, basal and squamous cell carcinomas are slow-growing and rarely metastasize (Stulberg et al., 2004). Since the prognosis of non-melanoma skin cancers is so much better than that of melanoma, it is critical that a distinction be maintained between the two in order to avoid confusion. Thus, the overarching term "skin cancer" is of limited usefulness. Even published papers forget to make the necessary distinction (e.g., Rivas et al., 2012).

Melanoma is most common in the elderly. The median age at melanoma diagnosis is 61, and the highest incidence is in people 55 to 64 years of age (National Cancer Institute, "SEER cancer statistics factsheets," n.d.). The median age for melanoma deaths is 69, and death rates for melanoma are highest in those 75 to 84 years of age (National Cancer Institute, "SEER cancer statistics factsheets," n.d.). Melanoma affects elderly people considerably more than young people, but it is quite prevalent among young people as compared to other cancers. It is the second most common cancer in adolescents and young adults under the age of 30 in the United States and the most common for those ages 25 to 29 (Weir et al., 2011; Skin Cancer Foundation, 2013).

Patterns of melanoma incidence differ markedly between males and females. Melanoma rates are considerably higher for men than women, with one in 35 males and one in 54 females acquiring melanoma in their lifetime (American Cancer Society, "Cancer facts and figures," 2013). Women under 40 are twice as likely to get melanoma as men, but after age 40 men have a higher rate and at 80 years and older the rate is three

times that in women the same age (American Cancer Society, "Cancer facts and figures," 2013). While younger women have a higher incidence of melanoma than men, young men often have more severe cases. For those ages 15 to 39, the higher melanoma incidence among women is confined to thin lesions, which are less than one millimeter thick (Jemal et al., 2011). Young men have a 55 percent lower survival rate than young women, comprising 40 percent of the cases but 60 percent of the deaths in ages 15 to 39 (Fisher and Geller, 2013).

Melanoma disproportionately affects Caucasian individuals, but other ethnicities have a larger proportion of severe and deadly cases (Gloster and Neal, 2006). Caucasians are twenty times more likely than African Americans to have a melanoma, but African Americans appear to have a greater ratio of melanoma to non-melanoma skin cancers than whites do (Gilchrest et al., 1999; Moan et al., 1999). Non-Caucasian patients often get diagnosed with melanoma at a more advanced stage of the disease. In a retrospective study of residents of Miami-Dade county, Florida, 52 percent of non-Hispanic black patients, 27 percent of Hispanic patients, and only 16 percent of non-Hispanic white patients received an initial diagnosis of late-stage melanoma (Hu et al., 2006). Moreover, non-Caucasians account for 6.5 percent of pediatric melanomas, which is a higher proportion than that in adults (Skin Cancer Foundation, 2013). Whereas melanomas in Caucasians most often appear on areas exposed to the sun, melanomas in African Americans, Asians, Filipinos, Indonesians, and Native Hawaiians generally occur on areas with less pigment and not often exposed to the sun, such as the skin of their nail beds, soles of the feet, palms, and mucous membranes (Gloster and Neal, 2006; Gilchrest et al., 1999).

It is unclear precisely how a normal melanocyte becomes a melanoma cell, but melanoma is thought to be preceded by an accumulation of mutations, many of which have been identified (Weir et al., 2011). Approximately 50 to 65 percent of melanomas have mutations that overactivate the BRAF gene, which codes for a protein involved in cell signaling and proliferation, and twenty percent of melanomas have mutant overactive NRAS, a GTPase involved in regulating cell division (National Institutes of Health, 2014; Uong and Zon, 2010). Since these mutations are found in melanoma tissue and the wild-type versions are found in normal tissue from the same patients, the mutations seem to be somatically acquired (Uong and Zon, 2010).

Other melanoma-associated mutations are heritable, such as germ-line mutations in the CDKN2A locus and certain variants in the polymorphic MC1R gene (Goldstein et al., 2005). CDKN2A is a prominent tumor suppressor gene, and MC1R codes for a hormone receptor and is significantly involved in pigmentation (National Institutes of Health, 2014). CDKN2A is considered a "high risk" mutation for melanoma production, and approximately twenty percent of melanoma patients have CDKN2A mutations (Goldstein et al., 2005). Though a "low risk" mutation for melanoma formation, variation in the MC1R gene is commonly seen in patients with melanomas (Goldstein et al., 2005). In a French study, loss-of-function MC1R variants were found in 68 percent of patients and only 31 percent of controls, thus illustrating that while such variants are common in normal individuals they are much more prevalent in those with melanomas (Matichard et al., 2004).

A major causal factor for most melanomas appears to be exposure to ultraviolet (UV) radiation, which is the most abundant environmental carcinogen (Bhattacharyya et

al., 2013). Ultraviolet radiation has been divided into three major categories based on wavelength: UVA (320 – 400 nm), UVB (290 – 320 nm), and UVC (less than 290 nm) (Ikehata and Ono, 2011). UVA is the weakest band and is known to cause premature aging in skin cells as well as indirect damage to DNA (American Cancer Society, "What is UV radiation?" 2013). UVB radiation is higher energy and directly damages the DNA in the skin, causes sunburn, and is thought to play more of a role in skin cancer formation than UVA (Skin Cancer Foundation, n.d.). The ozone layer completely blocks out UVC radiation, and in fact it filters out most UVB radiation but not UVA (World Health Organization, n.d.). Unlike the higher energy wavelengths of ionizing radiation, UVA and UVB radiation are not able to penetrate deeply into the body, and thus they primarily affect the skin (American Cancer Society, "What is UV radiation?" 2013). More specifically, UVB radiation almost exclusively impacts the epidermis while UVA affects the dermis and basal layer of the epidermis (Skin Cancer Foundation, n.d.). UVB, most often in the form of sunlight, has a strong tendency to damage DNA in the skin (Ikehata and Ono, 2011). Both UVA and UVB radiation introduce two types of DNA lesions into the double helix — cyclobutane pyrimidine dimers and 6-4 photoproducts — which hamper replication and transcription by causing kinks or bends in DNA (Clancy, 2008). Throughout most of the lifespan, humans' repair mechanisms are able to fix the damage via nucleotide excision repair and other methods (Clancy, 2008). However, when repair mechanisms fail, mutations may result, which could eventually lead to a melanoma. Throughout the remainder of this paper, "UV" refers to both UVA and UVB radiation unless otherwise specified.

The pattern of UV exposure also appears to have major implications for melanoma formation. Intermittent, rather than chronic or occupational exposure, seems to carry the greatest risk (Elwood and Jopson, 1997). Intermittent exposure is likely more dangerous because after absence from significant UV exposure, the skin has a lower melanin content, and thus the melanocytes are unprotected from the genotoxic effects of UV radiation (Gilchrest et al., 1999). It may be inferred that three weeks of absence from UV exposure is the period of time after which the skin starts to lose melanin content, since three weeks is how long a moderate tan persists in most people after being exposed to a single, sunburn-inducing dose of UV radiation (Gilchrest et al., 1999). In individuals who are able to tan, UV exposure stimulates melanin synthesis which persists for days, and it may take weeks or even months for the skin to return to its normal color (Brenner and Hearing, 2008). Thus, individuals who are exposed to the sun regularly and are able to tan have an enhanced degree of photoprotection (Brenner and Hearing, 2008). Additionally, many studies have shown a positive correlation between history of sunburn and melanoma (Gandini et al., 2005).

The average minimum ozone levels for 2013 (133 Dobson Units) were less than in 1979 (225 Dobson Units), the first year that comprehensive ozone measurements were available (National Aeronautics and Space Administration, 2014). The ozone layer has thinned due to ozone depletion caused largely by chlorine and bromine based chemicals, thus more UVB radiation reaches the ground than previously (National Aeronautics and Space Administration, 2014). In addition to the absorptive power of the ozone layer, another factor significantly affecting the UV intensity is the angle of the sun, and this is influenced by time of day, season, and latitude (U.S. Environmental Protection Agency,

2014). The sun is at its maximal angle for a given area at solar noon (i.e., when the sun is at its highest point) and during the summer months (University of California, Santa Barbara, n.d.). The angle of the sun at solar noon decreases with increasing latitudes (University of California, Santa Barbara, n.d.). Moreover, cloud cover and altitude help determine how much UV radiation reaches the ground (World Health Organization, n.d.). Scattered clouds transmit 89 percent of UV radiation, broken clouds allow 73 percent, and overcast skies transmit only 31 percent (Environmental Protection Agency, 2014). UV radiation reaching the ground increases roughly ten percent with every 1000 meter increase in altitude (World Health Organization, n.d.). In order to quantify many of the factors listed above into a single whole number which could be easily understood by the public, Canada introduced the UV index in 1992 (Fioletov et al., 2010). The UV index ranges from one (mild) to eleven or more (extreme), and it takes into account ozone levels, sunlight angle, cloud cover, and UV strength weighted towards the UV wavelengths that cause the most damage to human skin (Environmental Protection Agency, 2014).

Though there is a strong body of evidence suggesting that UV exposure helps bring about both melanoma and non-melanoma skin cancers, there is a dearth of studies offering an explicit quantitative relationship between UV strength and skin cancer incidence or a predictive equation based on those variables. However one Chilean paper offered simple, explicit predictive equations. In a study of Chilean skin cancer rates, Rivas et al. (2012) formed predictive equations relating latitude with skin cancer incidence [Skin Cancer Incidence = 45.718-0.753*(Latitude)], and accumulated UV index with skin cancer incidence [Skin Cancer Incidence = 5.019+0.336*(UV index)].

The Rivas equations were developed using incidence data that included both melanoma and non-melanoma skin cancers (Rivas, pers. comm., 2013).

In the absence of any useful predictive models for skin cancer for the United States, I sought to test the reliability of the Rivas equations in determining melanoma rates in the U.S. Melanoma incidence was used instead of general skin cancer incidence because non-melanoma skin cancers are not reported to cancer registries in the United States (Rogers et al., 2010). I developed the following null hypotheses: (1) The first Rivas equation relating skin cancer incidence and latitude does not have predictive power for United States melanoma incidence data; (2) The second Rivas equation relating skin cancer incidence and accumulated UV index does not have predictive power for United States melanoma incidence data; (3) Melanoma incidence rates for specific locations in the United States are unrelated to the latitudes of those locations; (4) Melanoma incidence rates for specific locations in the United States are unrelated to the accumulated UV index values for those locations.

MATERIALS AND METHODS

Data Sources

UV indices of cities across the country were obtained from National Oceanic and Atmospheric Administration (NOAA) National Weather Service "UV Index: Annual Time Series" (n.d.). Cities used in this study were those found in the NOAA (n.d.) UV index dataset. Average accumulated UV index for the years 2006 to 2010 was calculated for each city. Following Rivas's methodology, average accumulated UV index for a particular year is calculated by adding up the monthly means of the maximal daily UV index values (Rivas, pers. comm., 2013). This calculation was carried out for each year from 2006 to 2010, and the resulting values were averaged.

Latitudes were acquired for each city through Google Maps (2014). The city latitudes were used for melanoma incidence data that were specific to a county, city, or metropolitan area. For state-wide melanoma incidence data, I obtained the latitude of each state's geographic center from About.com Geography (Rosenberg, n.d.). Latitudes in degrees and minutes were converted to decimal form for easier graphing by dividing the minutes by 60.

Melanoma incidence refers to the rate per 100,000 inhabitants. The age-adjusted melanoma incidence data for each county encompassing each listed city were obtained from the Centers for Disease Control's (CDC) (2013) online tool "U.S. County Cancer Incidence Dataset" except for the county incidence data for Kansas, which was not available in that dataset, and Virginia, for which there was only statewide data in the dataset. The county melanoma incidence data for Kansas was obtained from the Kansas Cancer Registry (2012). Statewide melanoma incidence data from the CDC (2013) tool

was used for Virginia. Cities in the UV index dataset whose counties or states did not have melanoma incidence data on CDC's (2013) incidence dataset or data with the proper years (2006-2010) on their state cancer registry websites were excluded from the study. The majority of the cities were located wholly within a county and thus county-wide data is used for the listed cities. In some cases, a city was either its own county or an independent municipality. For cities located in more than one county, the most populous county was used. In the case of New York City, which is composed of five prominent counties, New York county (i.e., Manhattan) was selected because it is the nearest to the listed latitude of New York City. See Table 1 for a list of the specific counties and independent cities for which I found incidence data. For each area, I found melanoma incidence for both genders combined and separated for all ethnicities combined and for whites, Hispanic included. Even though this data includes incidence values from some independent cities as well as the statewide incidence for Virginia, I will refer to it as county melanoma incidence data.

With one exception, I obtained age-adjusted melanoma incidence data for a greater number of ethnicities using the "Fast Stats" tool from the North American Association of Central Cancer Registries (NAACCR) (2012). I used the New York Cancer Registry (2012) to acquire such data for Manhattan. Both NAACCR data and New York State Cancer Registry incidence data were for the years 2006 to 2010. The majority of the data was statewide, but I utilized metropolitan and city-specific data where available. Areas for which I found metropolitan or city-specific data are as follows: New York City, NY (Manhattan specific), Washington, D.C., San Francisco, CA, Los Angeles, CA, and Atlanta, GA.

Concerning statewide melanoma incidence data, the majority of states used had only one city with available UV index values. For these, I used the UV index data for the listed city. Texas, Florida, and Pennsylvania each had statewide melanoma incidence data, but they had multiple cities with UV index data. For these, I used the UV index data for the city closest to the state's geographic center.

With regard to each state, metropolitan area, or city, I found melanoma incidence for genders combined and separated for each of the following ethnicities: white non-Hispanic, Asian or Pacific Islander, African American, Hispanic, and American Indian or Alaska Native. In addition, I found age-specific melanoma incidence data for U.S. males and females from NAACCR (2012). The age groups are as follows: less than one, one to four, ages five to 84 in five year increments, and 85 and older.

Data Analyses

The following data analyses were all performed in Microsoft Excel 2010®. Unless otherwise specified, melanoma incidence encompasses both genders and all ethnicities. Estimated skin cancer incidence rates were calculated by entering U.S. city latitudes and accumulated UV index values into the first and second Rivas equations, respectively. For each equation, a simple linear regression analysis was performed of melanoma incidence (using county melanoma incidence data) against estimated skin cancer incidence.

In order to examine the strength of the relationship of accumulated UV index and latitude in the United States, a simple linear regression analysis was performed of average accumulated UV index, 2006-2010, against city latitude. For Virginia, the latitude of the state geographic center was used instead. Simple linear regression analyses of melanoma

incidence against accumulated UV index and melanoma incidence against latitude were carried out in order to separately evaluate the relationship of each variable with melanoma incidence. A simple linear regression analysis was performed of melanoma incidence against male melanoma incidence to investigate the contribution of males to the total melanoma incidence. A simple linear regression analysis of female melanoma incidence against latitude was carried out to see if female incidence had a different relationship with latitude than the total melanoma incidence. The following multiple linear regressions were carried out in order to investigate possible differences in the relationships between accumulated UV index, latitude, and melanoma incidence among varying demographic groups. Multiple linear regression analyses were performed for melanoma incidence and white including Hispanic melanoma incidence (genders combined and separated), respectively, against accumulated UV index and latitude. The preceding regression analyses all used county melanoma incidence data. For the state, city, and metropolitan data from NAACCR (2012) and the New York Cancer Registry (2012), multiple regression analyses were performed for melanoma incidence data (genders combined and separated) of the following demographic groups against accumulated UV index and latitude: white non-Hispanic, Asian or Pacific Islander, African American, Hispanic, and American Indian or Alaska Native.

RESULTS

The melanoma incidence data had a significant relationship with the estimated skin cancer incidence produced by the first Rivas equation (Figure 1) and a nearly significant relationship with that of the second Rivas equation (Figure 2). Simple linear regression analyses revealed significant relationships in the following pairs of variables: accumulated UV index and latitude (Figure 3); melanoma incidence and male melanoma incidence (Figure 4); melanoma incidence and latitude (Figure 5); female melanoma incidence and latitude (Figure 6). The simple linear regression analysis of melanoma incidence against accumulated UV index showed a nearly significant relationship between the two variables (Figure 7). Multiple regression analyses using county data revealed insignificant relationships of melanoma incidence with accumulated UV index and latitude for all groups (Table 2).

Multiple regression analyses using state, city, and metropolitan data revealed a statistically significant or nearly significant relationship of melanoma incidence against accumulated UV index and latitude in American Indian or Alaska Native combined gender (Figure 8), male (Figure 9), and female (Figure 10). The melanoma incidence rates of the remaining demographic groups displayed insignificant relationships with accumulated UV index and latitude (Table 3).

On the age group graph (Figure 11), females had a higher melanoma incidence than men until 50-54, after which point the male rates surpassed them. The rate for females increases steadily until 85 and older, when the rate shows a slight decrease. The male incidence rates increase much more rapidly throughout life, and each age group has a significantly higher incidence than the preceding one.

DISCUSSION

Though the skin cancer incidence values predicted by the first Rivas equation had a significant relationship with U.S. melanoma incidence, the correlation was weak due to a low r^2 value. Furthermore, the first Rivas equation predicted a negative value for incidence at one point, which is an undesirable result since incidence by nature cannot be negative. The first Rivas equation may be an unreliable predictor in part because it was designed from only four data points (Rivas et al., 2012). The skin cancer incidence predicted by the second Rivas equation also had a weak relationship with U.S. melanoma incidence as evidenced by the low r^2 value. The second Rivas equation was designed from fourteen data points, which is likely still too few to form a reliable predictive equation (Rivas et al., 2012). One would expect Figures 1 and 2 to both show positive rather than negative relationships since melanoma and skin cancer rates would be expected to be positively correlated. However, the main importance of each graph is that they show the Rivas equations do not work well to predict melanoma rates in the U.S. Because the r^2 values are so low in both figures, the direction of the linear fit is not very meaningful. The Rivas equations were designed with general skin cancer incidence data, so perhaps if U.S. general skin cancer incidence had been available to use, the results would have been more highly correlated. Since the Rivas equations were poor predictors for melanoma rates in the U.S., the first two null hypotheses were not rejected.

Accumulated UV index and latitude were shown to have a significant and strong inverse relationship, which corroborates the idea that lower latitudes receive higher UV levels. Male melanoma incidence had a strong relationship with melanoma incidence. It seems likely that males have a greater total contribution to overall melanoma incidence

due to the higher rates for males, but it would be helpful to carry out a simple linear regression analysis of melanoma incidence against female melanoma incidence in order to verify this hypothesis. The relationship of melanoma incidence against latitude was marked by a low r^2 value, whereas the regression of female melanoma incidence against latitude had a higher r^2 value. This may suggest that female melanoma incidence occurs more along a latitude gradient than that of males, but a simple linear regression analysis of male melanoma incidence against latitude should be carried out in order to substantiate this hypothesis.

Across all demographic groups except American Indian or Alaska Native, data were marked by poor relationships between incidence, accumulated UV index, and latitude. The third and fourth null hypotheses were only rejected by the data for the American Indian or Alaska Native ethnicity category. The combined gender American Indian or Alaska Native contained somewhat strong relationships with accumulated UV index and latitude as seen by their moderate r^2 values. Female American Indian or Alaska Native melanoma incidence had a strong correlation between the variables due to a high r^2 value but the relationship was not quite significant. This lack of significance may have stemmed from the fact that there were only six data points for female American Indian or Alaska Native melanoma incidence, which is less than that of either combined gender ($n = 11$) or male ($n = 8$) incidence for that demographic group. Perhaps American Indians and Alaska Native males and females have somewhat homogeneous habits of sun exposure and sun protection stemming from a relative uniformity of lifestyle. Moreover, they may be more prone to live in one location throughout life and may travel less frequently than other demographic groups. The previous two hypotheses, if statistically

supported, may account for a reduction in confounding variables in the data, and thus a stronger relationship between melanoma incidence, latitude, and accumulated UV index.

Male and female melanoma incidence rates in the U.S. may differ due to behavioral and biological differences. The higher melanoma rates of females in their teens and twenties may be related to the fact that adolescent girls are more likely than other groups to tan indoors (Buller et al., 2011). Conversely, females tend to engage in sun-protective behaviors more often than males, which may explain the higher rates in males later in life (Buller et al., 2011). Furthermore, there may be differences between the sexes in biological traits such as skin thickness or melanocyte physiology which might contribute to the different rate patterns.

The lack of a significant correlation between melanoma incidence, accumulated UV index, and latitude does not rule out UV exposure as a major risk factor for melanoma. Indeed, since intermittent patterns of UV exposure seem to carry a higher melanoma risk than chronic patterns, one would not expect there to be a clear correlation between incidence and the other two variables. Since those in areas of higher latitude and lower average UV index would historically have less melanin than those in areas of greater sun exposure, they are less protected from UV radiation. Thus, when those individuals with lower amounts of melanin receive a high dose of UV radiation on an unusually bright day, a vacation to a tropical area, or hours in a tanning bed, their melanocytes are more vulnerable to UV damage than individuals who have been more regularly exposed. Indeed, Elwood and Diffey (1993) calculated that individuals at higher latitudes (50 to 55^{o} N) receive 33 percent of their total UVB exposure as

intermittent exposure while those at lower latitudes (15 to 27^{o} S) receive only 23 percent as intermittent exposure.

This study had several limitations. Movement of peoples was not accounted for, namely immigration and vacations. It is possible that a person may have received the bulk of his or her UV exposure from previous locations before moving to the location where he or she received the diagnosis. Furthermore, people in high latitudes with low UV levels may receive a large amount of their exposure from vacations in sunnier areas. Another major factor which this study did not fully account for is genetic variation. Some populations, even within the same listed ethnic group, may naturally have skin with higher melanin content than others. For instance, areas with a large concentration of inhabitants of Nordic or Scots-Irish ancestry may have significantly different rates than those with large populations of Mediterranean ancestry, but these populations would all be listed in the cancer registries as non-Hispanic white. Perhaps the largest setback for this and any similar study is the possibility that melanoma diagnoses are considerably under-reported by physicians. A survey administered to dermatologists attending the Cutaneous Oncology Symposium in 2010 found that 50 percent of the respondents did not know they were obligated to report new melanoma diagnoses to their state cancer registry, and 56 percent did not report or did not know how to report the new diagnoses (Cartee et al., 2011). Since many melanoma cases may go unreported, it is possible that the rates of reporting diagnoses vary in different areas. Thus, any study comparing melanoma incidence rates between areas faces a serious disadvantage.

More reliable sun exposure and behavioral data is needed before any definite conclusions can be formed about the relationship of UV exposure to melanoma rates.

Future studies may do well to incorporate data from wearable fitness devices that track information such as steps and miles. The popularity of such devices is growing, and nine percent of people owned a wearable fitness device in 2013 (Dahl, 2014). Studies could use data from the devices of active users to measure time spent in the sun in order to make a more accurate estimate of UV exposure. However, in order to ensure that future melanoma studies are meaningful, dermatologists must report all melanoma diagnoses to the state cancer registries. Perhaps this could be achieved by more thorough education of the responsibility to report to registries in dermatology residency programs for upcoming dermatologists and through continuing medical education for currently practicing ones.

The relationship of melanoma formation to UV exposure is complex, but it merits further research. Melanoma is one of the most common cancers, it can frequently be deadly, and its incidence is growing, with rates rising an average of 2.6 percent a year for the past ten years (National Cancer Institute, "SEER cancer statistics factsheets," n.d.). Groundbreaking new treatments for advanced stage melanoma such as molecularly targeted treatments and immunotherapies provide a more promising future for melanoma patients, but more work is desperately needed on the prevention front (Melanoma Research Alliance, n.d.). In order to effectively address this worrisome increasing incidence trend and provide accurate prevention information to the public, the scientific community needs to gain a more complete understanding of how UV exposure affects melanoma formation. As shown by this study, simple relationships between melanoma rates and UV exposure may not exist. A more nuanced approach which takes into account a number of demographic, behavioral, and environmental factors is warranted.

Table 1. List of counties used for county-specific melanoma incidence data. The boxes with a dash are for cities which are independent or have the same boundaries as the county.

City	County
Mobile, AL	Mobile
Anchorage, AK	-
Phoenix, AZ	Maricopa
Little Rock, AR	Pulaski
Los Angeles, CA	Los Angeles
San Francisco, CA	-
Denver, CO	-
Hartford, CT	Hartford
Washington, DC	-
Dover, DE	Kent
Jacksonville, FL	Duval
Miami, FL	Miami-Dade
Tampa, FL	Hillsborough
Atlanta, GA	Fulton
Honolulu, HI	-
Boise, ID	Ada
Chicago, IL	Cook
Indianapolis, IN	Marion
Des Moines, IA	Polk
Wichita, KS	Sedgwick
Louisville, KY	Jefferson
New Orleans, LA	-
Baltimore, MD	-
Boston, MA	Suffolk
Detroit, MI	Wayne
Jackson, MS	Hinds
St. Louis, MO	-
Billings, MT	Yellowstone
Omaha, NE	Douglas
Las Vegas, NV	Clark
Concord, NH	Merrimack
Atlantic City, NJ	Atlantic
Albuquerque, NM	Bernalillo
Buffalo, NY	Erie
New York City, NY	New York
Raleigh, NC	Wake
Bismarck, ND	Burleigh
Oklahoma City, OK	Oklahoma

Table 1 (cont.).

Portland, OR	Multnomah
Philadelphia, PA	-
Pittsburgh, PA	Allegheny
Providence, RI	Providence
Charleston, SC	Charleston
Sioux Falls, SD	Minnehaha
Memphis, TN	Shelby
Dallas, TX	Dallas
Houston, TX	Harris
Salt Lake City, UT	Salt Lake
Burlington, VT	Chittenden
Norfolk, VA	***statewide data used***
Seattle, WA	King
Charleston, WV	Kanawha
Milwaukee, WI	Milwaukee
Cheyenne, WY	Laramie

Table 2. Results of the multiple regression analysis of age-adjusted melanoma incidence per 100,000 of varying demographic groups against average accumulated UV index, 2006-2010, and latitude. County melanoma incidence data, 2006-2010.

Variables	**F-stat**	**P-value$_{UVI}$**	**P-value$_{Latitude}$**	**r^2**
Combined gender, Combined ethnicity	2.10	0.742	0.2976	0.0760
Combined gender, White incl. Hispanic	0.729	0.899	0.747	0.0278
Male, White incl. Hispanic	2.44	0.707	0.655	0.0874
Female, White incl. Hispanic	0.136	0.633	0.711	0.00530

Table 3. Results of the multiple regression analysis of age-adjusted melanoma incidence per 100,000 of varying demographic groups against average accumulated UV index, 2006-2010, and latitude. State and metropolitan melanoma incidence data, 2006-2010.

Variables	**F-stat**	**P-value$_{UVI}$**	**P-value$_{Latitude}$**	**r^2**
Combined gender, White non-Hispanic	6.62	0.0646	0.554	0.231
Male, White non-Hispanic	9.17	0.0396	0.380	0.290
Female, White non-Hispanic	3.02	0.364	0.412	0.118
Combined gender, Asian or Pacific Islander	0.272	0.704	0.845	0.0252
Male, Asian or Pacific Islander	0.491	0.697	0.534	0.0702
Female, Asian or Pacific Islander	0.238	0.905	0.959	0.0296
Combined gender, African American	0.429	0.544	0.947	0.0287
Male, African American	0.731	0.572	0.890	0.0574
Female, African American	0.288	0.518	0.771	0.0217
Combined gender, Hispanic	0.0256	0.855	0.825	0.00142
Male, Hispanic	0.0722	0.989	0.786	0.00436
Female, Hispanic	0.0841	0.764	0.984	0.00478

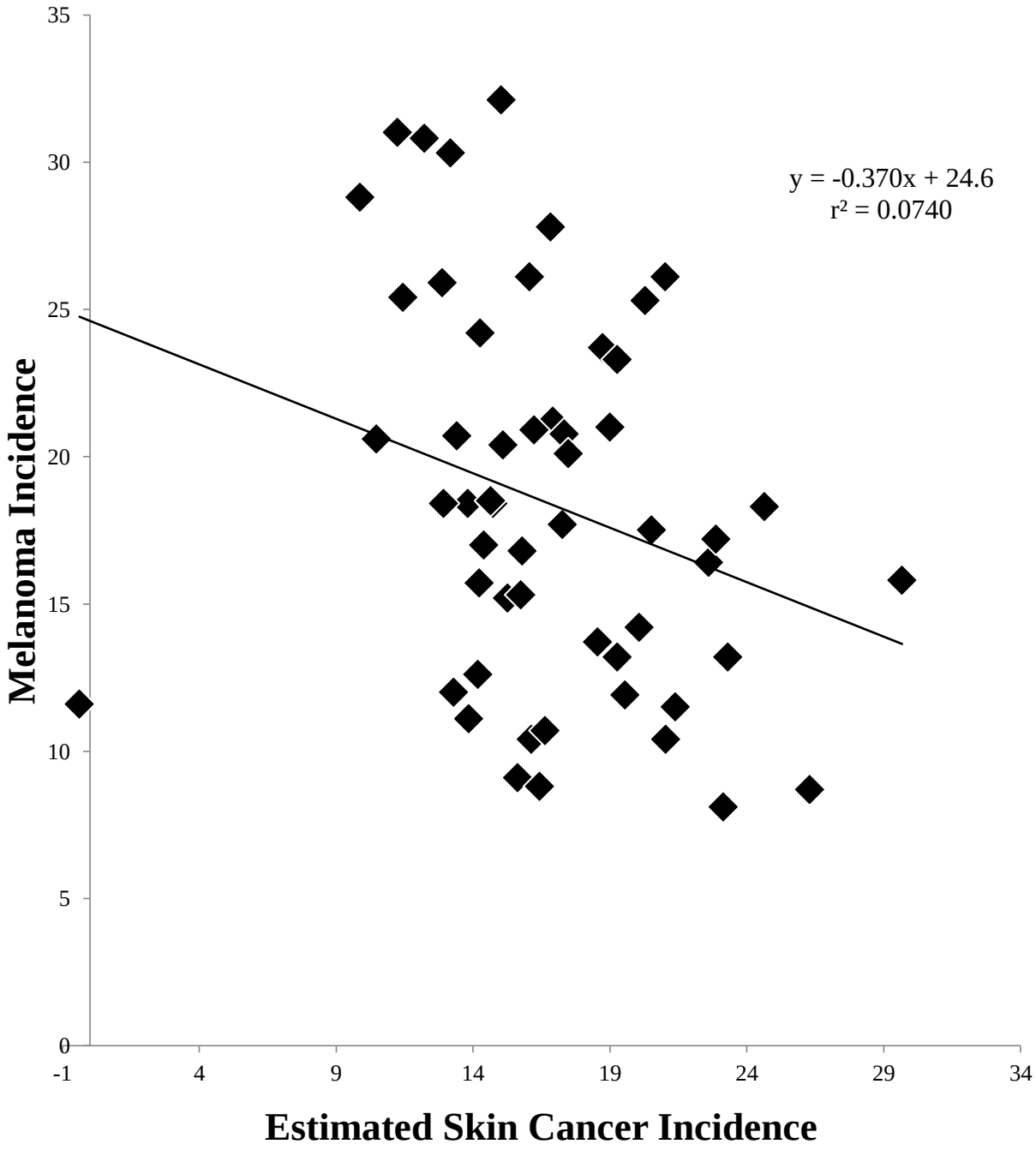

Figure 1. Simple linear regression of age-adjusted melanoma incidence per 100,000 inhabitants against skin cancer incidence estimated via 1st Rivas equation [Skin Cancer Incidence = 45.718-0.753*(Latitude)]. County melanoma incidence data, 2006-2010. F = 4.16, p = 0.0466.

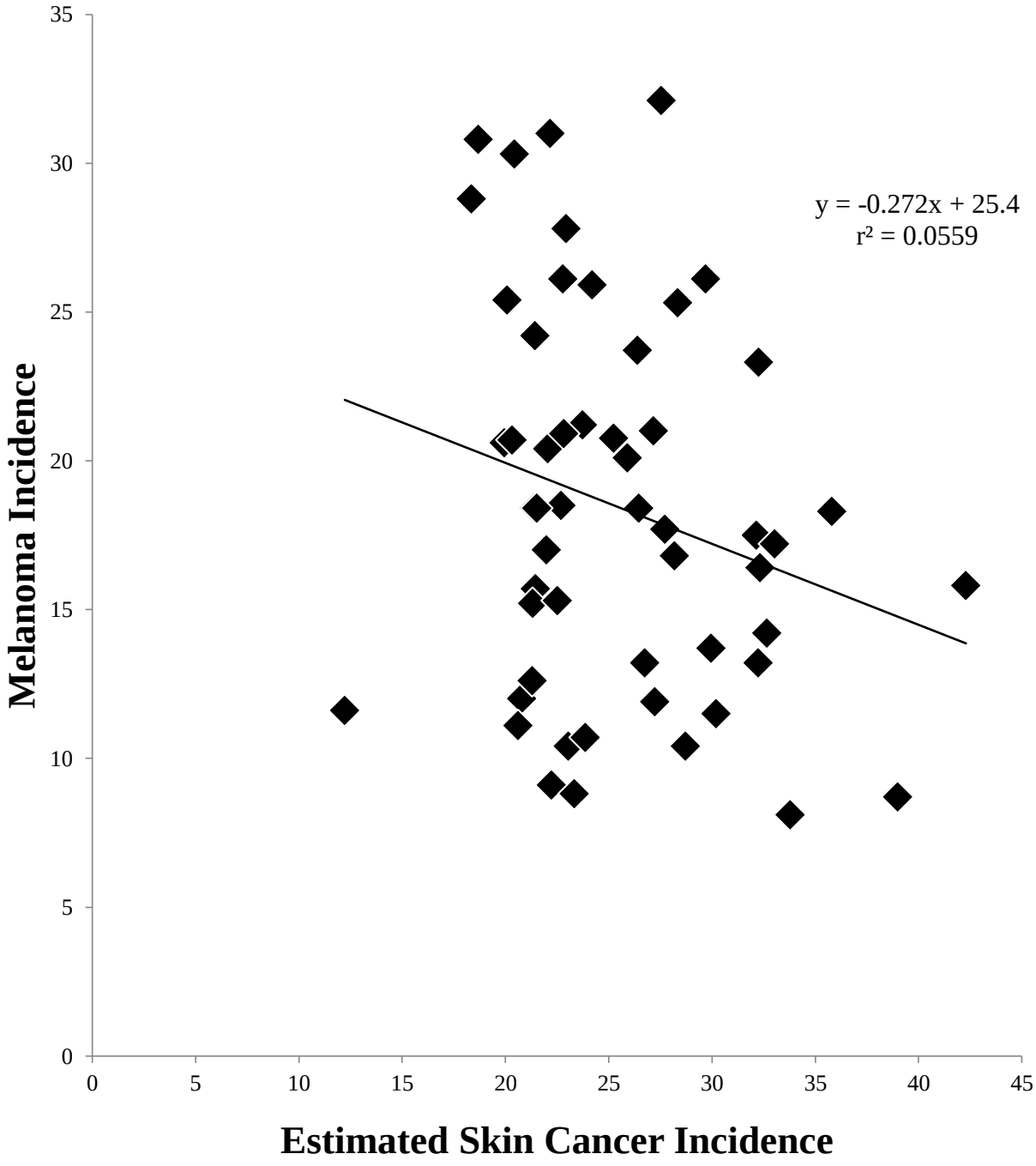

Figure 2. Simple linear regression of age-adjusted melanoma incidence per 100,000 inhabitants against skin cancer incidence estimated via 2nd Rivas equation [Skin Cancer Incidence = 5.019+0.336*(UV index)]. County melanoma incidence data, 2006-2010. F = 3.07, p = 0.0851.

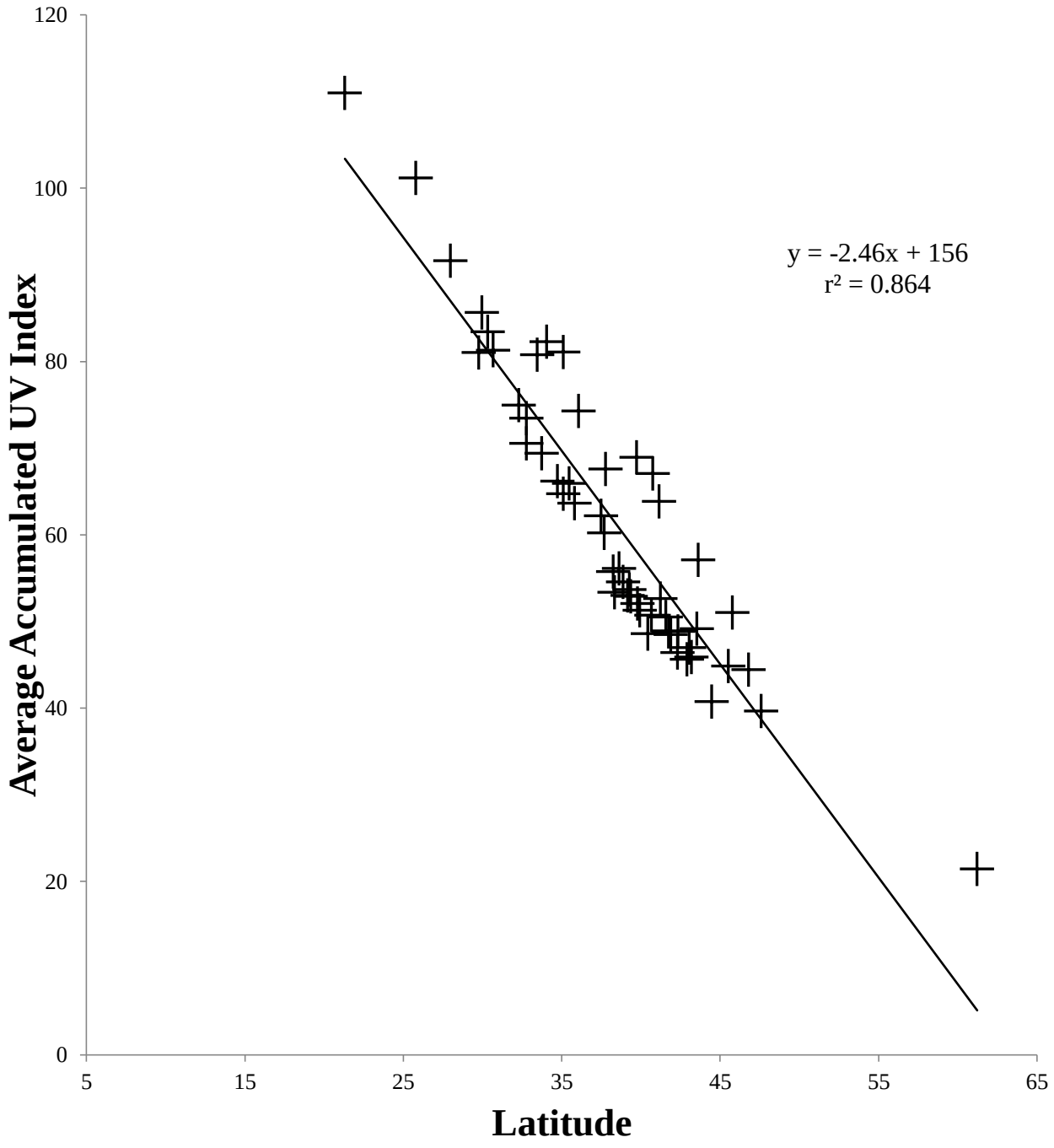

Figure 3. Simple linear regression of average accumulated UV Index, 2006-2010, against latitude. $F = 331$, $p = 3.33 \times 10^{-24}$.

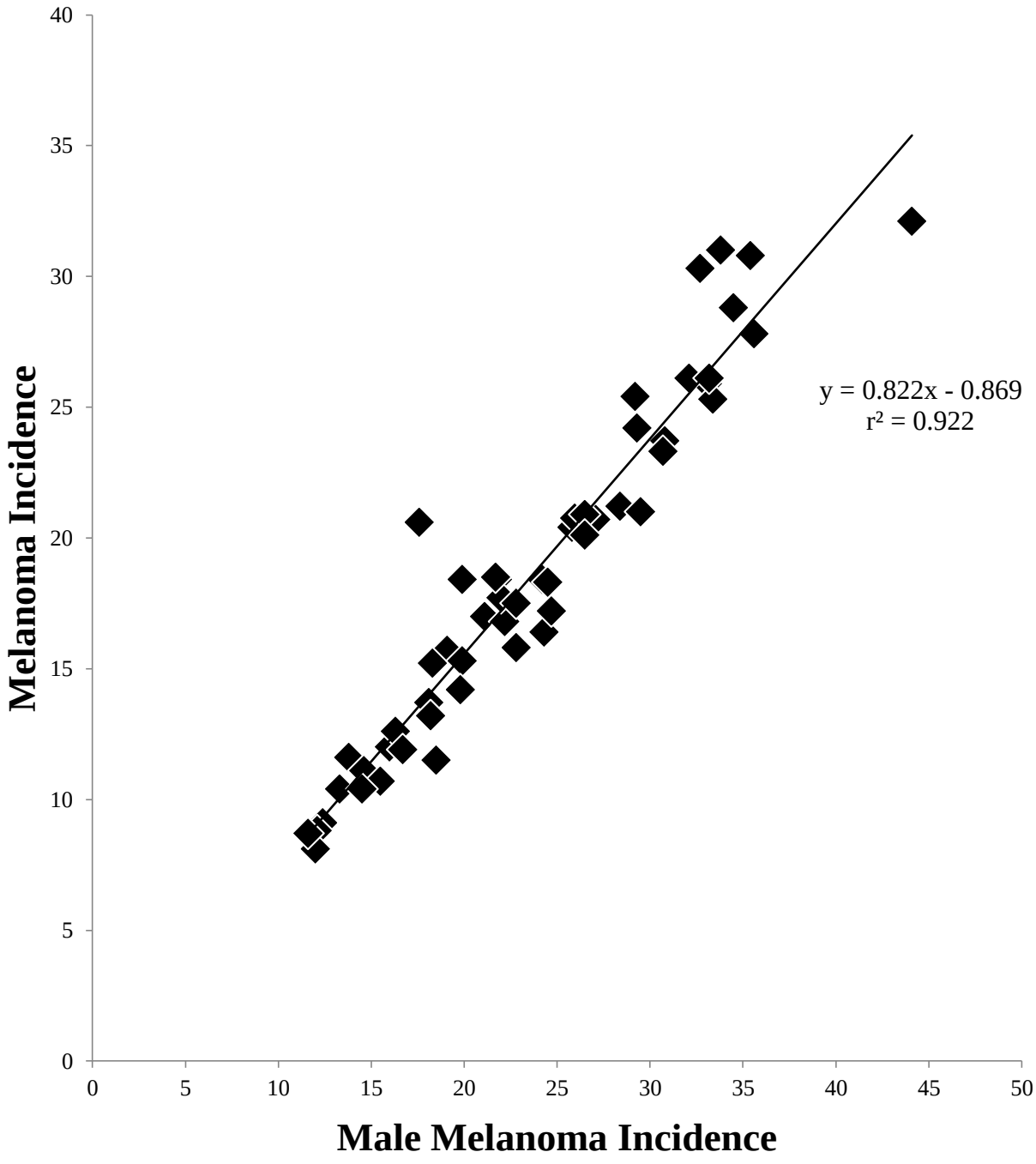

Figure 4. Simple linear regression of age-adjusted melanoma incidence per 100,000 inhabitants against age-adjusted male melanoma incidence per 100,000 inhabitants. County melanoma incidence data, 2006-2010. $F = 616$, $p = 1.7 \times 10^{-30}$.

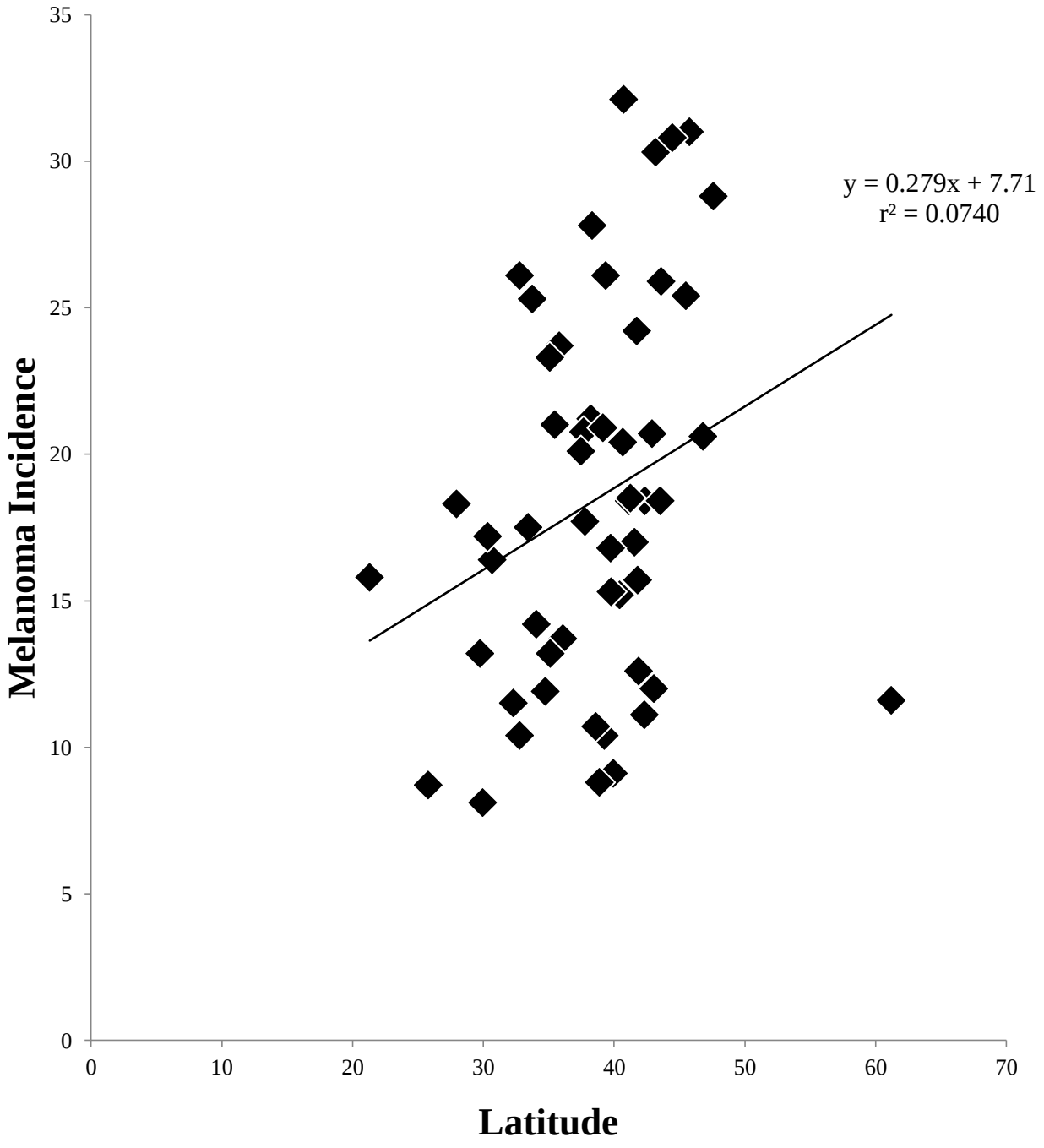

Figure 5. Simple linear regression of age-adjusted melanoma incidence per 100,000 inhabitants against latitude. County melanoma incidence data, 2006-2010. F = 4.16, p = 0.0466.

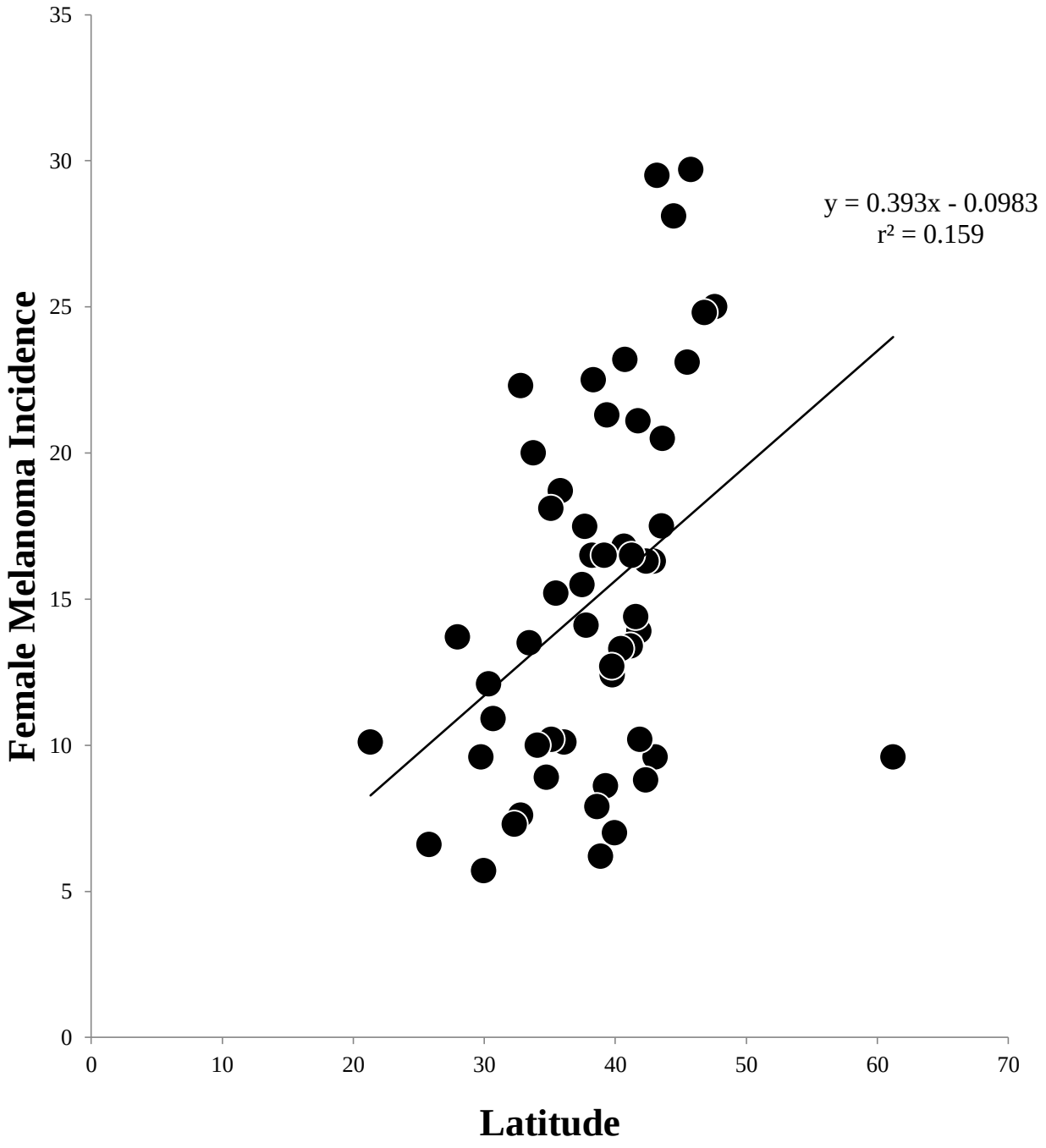

Figure 6. Simple linear regression of age-adjusted female melanoma incidence per 100,000 inhabitants against latitude. County melanoma incidence data, 2006-2010. F = 9.80, p = 0.00286.

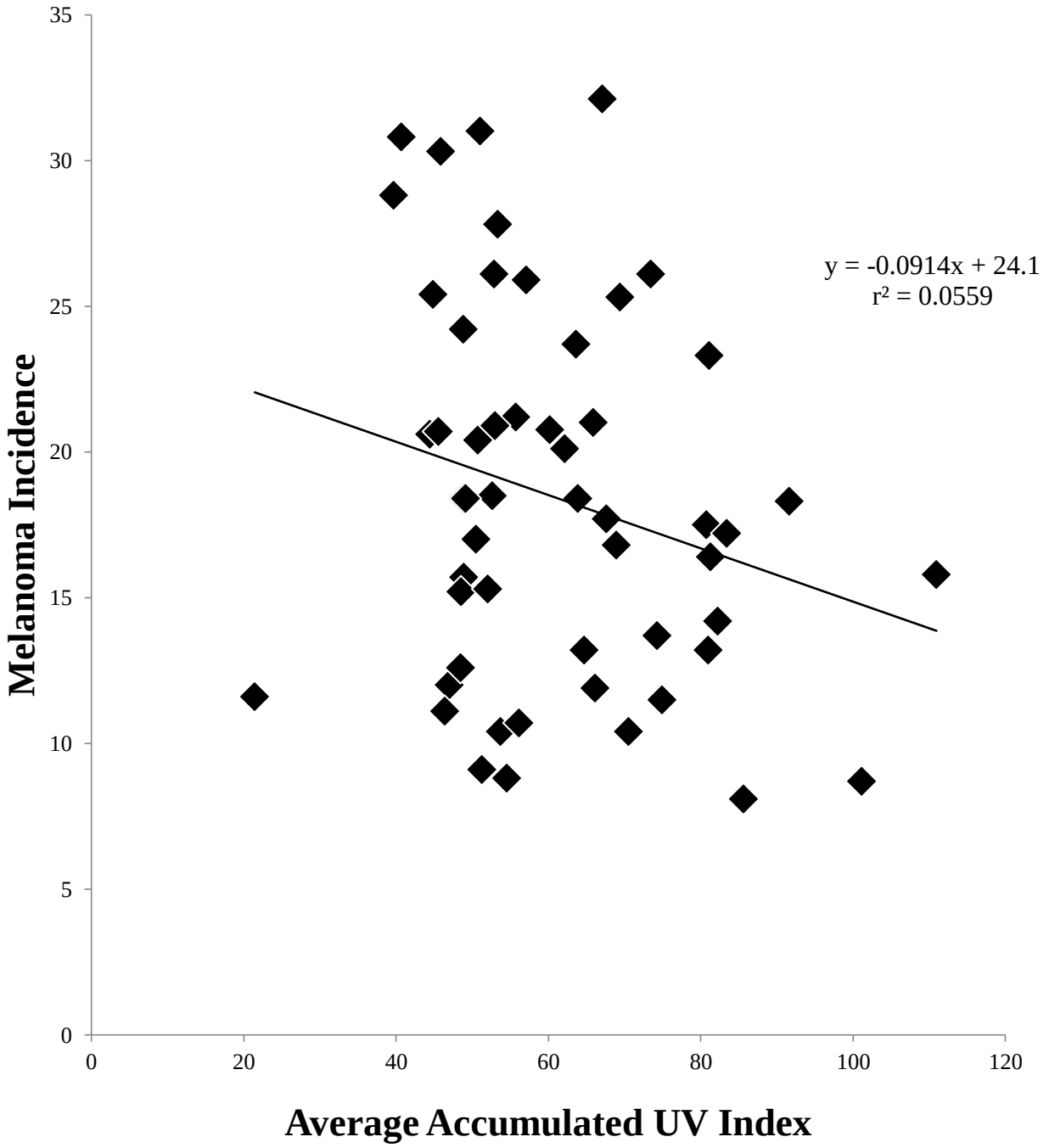

Figure 7. Simple linear regression of age-adjusted melanoma incidence per 100,000 inhabitants against average accumulated UV index, 2006-2010. County melanoma incidence data, 2006-2010. F = 3.08, p = 0.0851.

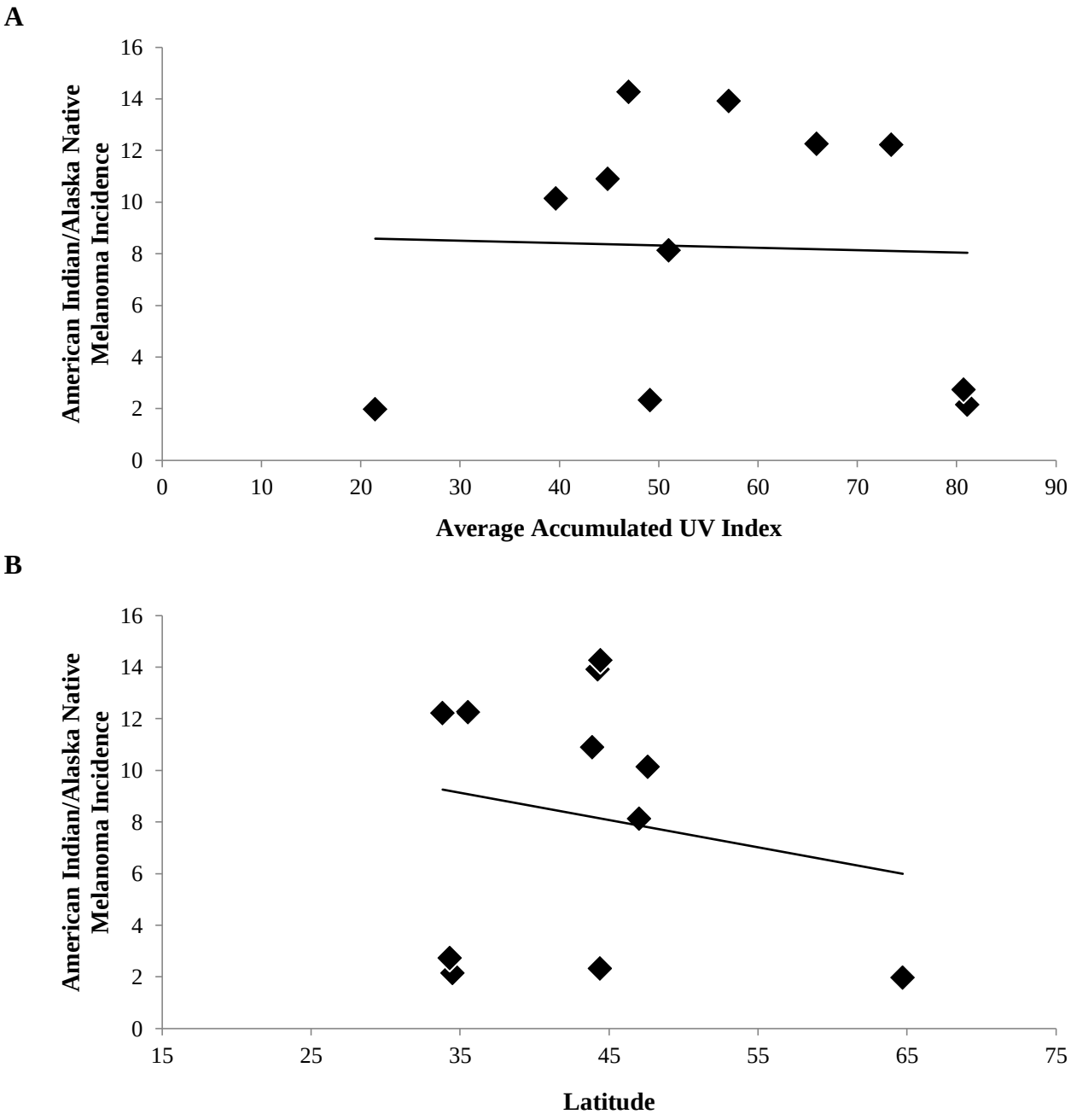

Figure 8. Multiple linear regression of age-adjusted American Indian or Alaska Native melanoma incidence per 100,000 inhabitants against (a) average accumulated UV index, 2006-2010: p = 0.0698 (b) latitude: p = 0.0594. $y = -0.446x_1 - 0.959x_2 + 74.4$, $r^2 = 0.377$, F = 2.42.

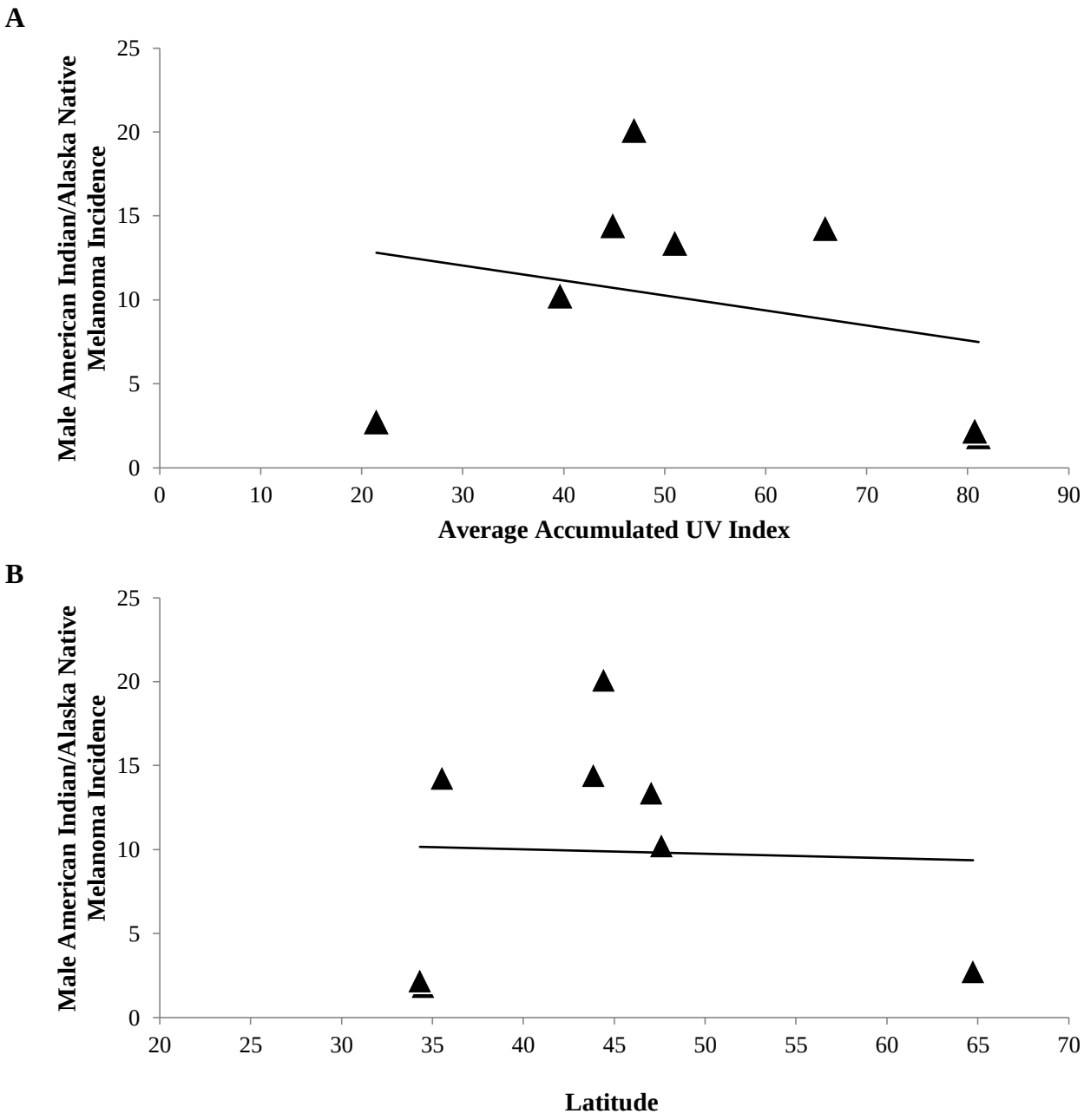

Figure 9. Multiple linear regression of age-adjusted male American Indian or Alaska Native melanoma incidence per 100,000 inhabitants against (a) average accumulated UV index, 2006-2010: p = 0.0217 (b) latitude: p = 0.0263. $y = -0.747x_1 - 1.46x_2 + 114$, $r^2 = 0.685$, F = 5.43.

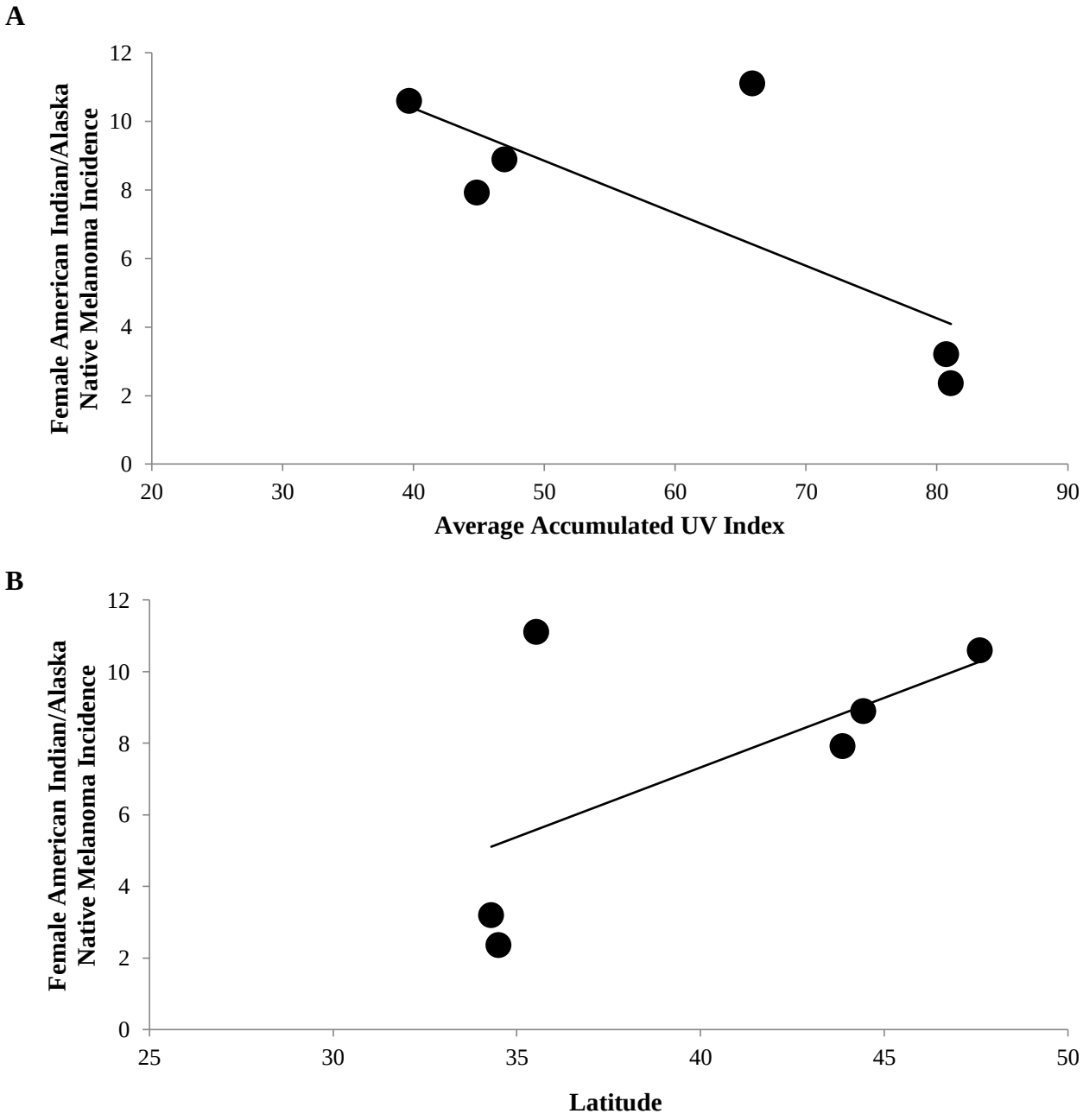

Figure 10. Multiple linear regression of age-adjusted female American Indian or Alaska Native melanoma incidence per 100,000 inhabitants against (a) average accumulated UV index, 2006-2010: p = 0.0774 (b) latitude: p = 0.148. $y = -0.525x_1 - 1.21x_2 + 87.1$, $r^2 = 0.814$, F = 6.57.

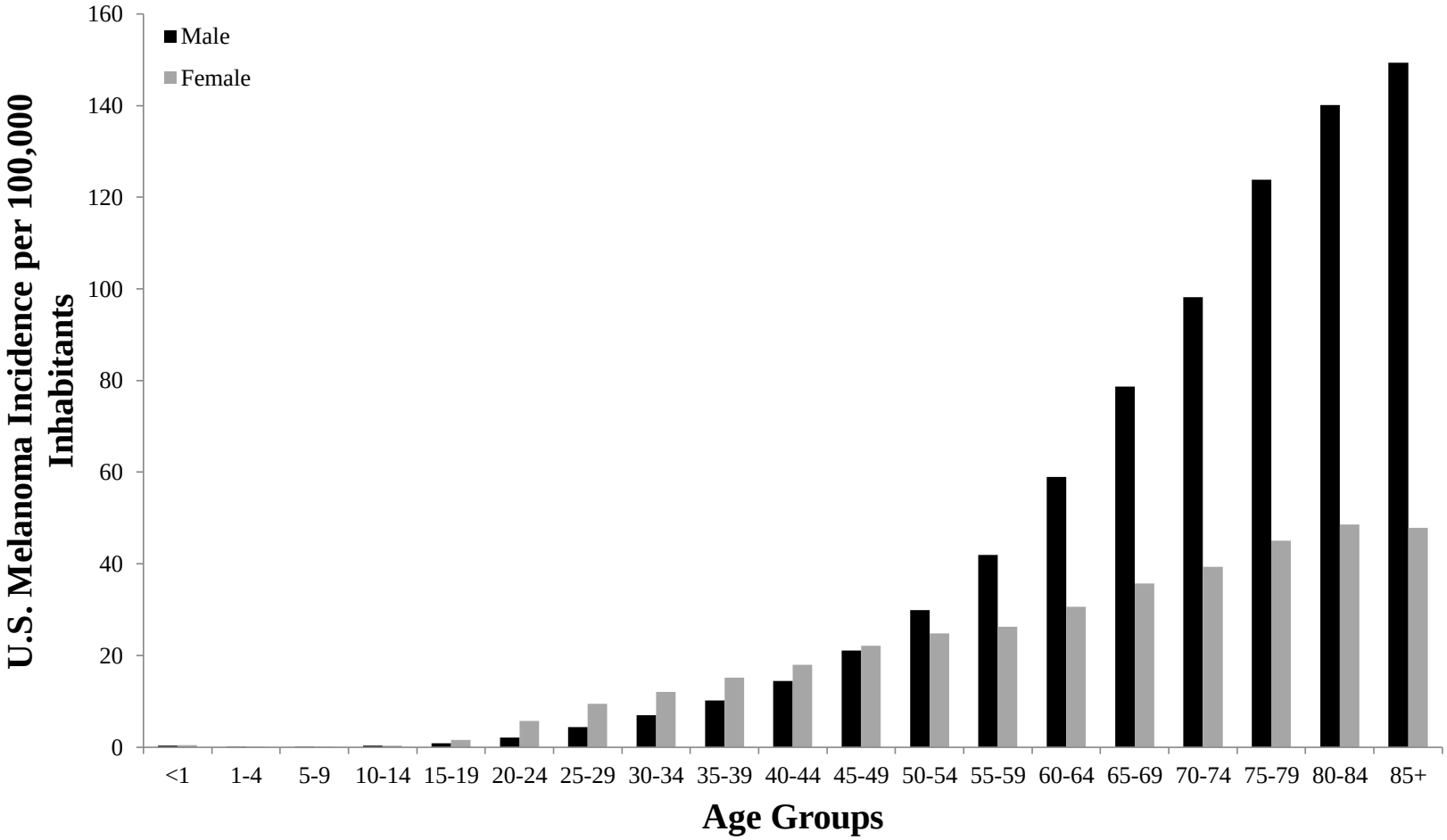

Figure 11. A plot of age-specific United States melanoma rates by age group per 100,000 inhabitants for males and females. Country-wide melanoma incidence data, 2006-2010.

LIST OF REFERENCES

American Academy of Dermatology (n.d.). Melanoma. <http://www.aad.org/media-resources/stats-and-facts/conditions/melanoma>. Accessed 9 February 2014.

American Cancer Society (2013). What is UV radiation? <http://www.cancer.org/cancer/ cancercauses/radiationexposureandcancer/uvradiation/uv-radiation-what-is-uv >. Accessed 14 March 2014.

American Cancer Society (2013). Cancer facts and figures 2013. <http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf>. Accessed 20 February 2014.

American Cancer Society (2014). Melanoma skin cancer. < http://www.cancer.org/acs/groups/cid/documents/webcontent/003120-pdf.pdf >. Accessed 7 February 2014.

Bhattacharyya, T., Barch, B.E., Vargas, M., and Thomas, J.R. (2013). Cutaneous injury following acute UV-B radiation in a mouse model: a pilot histological study. The Journal of Histotechnology 36, 37-44.

Brenner, M. and Hearing, V.J. (2008). The protective role of melanin against UV damage in human skin. Photochem. Photobiol. 84, 539-549.

Buller, D.B., Cokkinides, V., Hall, I., Hartman, A.M., Saraiya, M., Miller, E., Paddock, L., and Glanz, K. (2011). Prevalence of sunburn, sun protection, and indoor tanning behaviors among Americans: Review from national surveys and case studies of 3 states. J. Am. Acad. Dermatol. 65, S114.e1-11.

Cartee, T.V., Seema, P.K., and Suephy, C.C. (2011). Melanoma reporting to central cancer registries by US dermatologists: An analysis of the persistent knowledge and practice gap. J. Am. Acad. Dermatol. 65, S124.e1-9.

Center for Disease Control (2013). U.S. county cancer incidence dataset. < http://www.statecancerprofiles.cancer.gov/incidencerates/>. Accessed 1 January 2014.

Clancy, S. (2008). DNA damage and repair: mechanisms for maintaining DNA integrity. Nature Education 1, 103.

Dahl, M. (2014). Healthy or TMI? What do you do with all that fitness data? <http://www.nbcnews.com/health/diet-fitness/healthy-or-tmi-what-do-you-do-all-fitness-data-n11806>. Accessed 21 January 2014.

Eckert, R.L. and Rorke, E.A. (1989). Molecular biology of keratinocyte differentiation. Environmental Health Perspectives 80, 109-116.

Elwood, J.M. and Diffey, B.L. (1993). A consideration of ambient solar ultraviolet radiation in the interpretation of studies of the aetiology of melanoma. Melanoma Res. 3, 113-22.

Elwood, J.M. and Jopson, J. (1997). Melanoma and sun exposure: an overview of published studies. Int. J. Cancer 73, 198-203.

Environmental Protection Agency (2014). Calculating the UV index. <http://www2.epa.gov/sunwise/calculating-uv-index>. Accessed 25 February 2014.

Fioletov, V., Kerr, J.B., and Fergusson, A. (2010). The UV index: definition, distribution and factors affecting it. Can. J. Public Health 101, I5-9.

Fisher, D.E., Geller, A.C. (2013). Disproportionate burden of melanoma mortality in young US men. JAMA Dermatol. 149, 903-904.

Gandini, S., Sera, F., Cattaruzza, M.S., Pasquini, P., Picconi, O., Boyle, P., and Melchi, C.F. (2005). Meta-analysis of risk factors for cutaneous melanoma: II. Sun Exposure. European Journal of Cancer 41, 45-60.

Gilchrest, B.A., Eller, M.S., Geller, A.C., and Yaar, M. (1999). The Pathogenesis of Melanoma Induced by Ultraviolet Radiation. The New England Journal of Medicine 340, 1341-1348.

Gloster, H.M. and Neal, K. (2006). Skin cancer in skin of color. J. Am. Acad. Dermatol. 55, 741-760.

Goldstein, A.M., Landi, M.T., Tsang, S., Fraser, M.C., Munroe, D.J., and Tucker, M.A. (2005). Association of MC1R variants and risk of melanoma in melanoma-prone families with CDKN2A mutations. Cancer Epidemiol. Biomarkers. Prev. 14, 2208-2212.

Google Maps (2014). <maps.google.com>. Accessed 14 March 2014.

Hearing, V.J. (2011). Milestones in melanocytes/melanogenesis. J. Invest. Dermatol. 131, E1.

Hu, S., Soza-Vento, R.M., Parker, D.F., and Kirsner, R.S. (2006). Comparison of stage at diagnosis of melanoma among Hispanic, black, and white Patients in Miami-Dade County, Florida. Arch. Dermatol. 142, 704-708.

Ikehata, H. and Ono, T. (2011). The mechanisms of UV mutagenesis. J. Radiat. Res. 52, 115-125.

Jemal, A., Saraiya, M., Patel, P., Cherala, S.S., Barnholtz-Sloan, J., Kim, J., Wiggins, C.L., and Wingo, P.A. (2011). Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992 – 2006. J. Am. Acad. Dermatol. 65, S17.e1-11.

Matichard, E., Verpillat, P., Meziani, R., Gerard, B., Descamps, V., Legroux, E., Burnouf, M., Bertrand, G., Bouscarat, F., Archimbaud, A., Picard, C., Ollivaud,

L., Basset-Seguin, N., Kerob, D., Lanternier, G., Lebbe, C., Crickx, B., Grandchamp, B., and Soufir, N. (2004). Melanocortin 1 receptor (MC1R) gene variants may increase the risk of melanoma in France independently of clinical risk factors and UV exposure. J. Med. Genet. 41, 1-8.

Melanoma Research Alliance (n.d.). What is melanoma. <http://www.curemelanoma.org/about-melanoma/what-is-melanoma/>. Accessed 25 March 2014.

Moan, J., Dahlback, A., and Setlow, R.B. (1999). Epidemiological support for an hypothesis for melanoma induction indicating a role for UVA radiation. Photochem. Photobiol. 70, 243-247.

National Aeronautics and Space Administration (2014). Ozone Hole Watch. < http://ozonewatch.gsfc.nasa.gov/>. Accessed 14 March 2014.

National Cancer Institute (n.d.). Surveillance, Epidemiology, and End Results (SEER) cancer statistics factsheets: Melanoma of the skin. <http://seer.cancer.gov/statfacts/html/melan.html>. Accessed 14 March 2014.

National Cancer Institute (n.d.). Stages of melanoma. <http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/Patient/page2#Keypoint14>. Accessed 14 March 2014.

National Institutes of Health (2014). Genetics home reference. <http://ghr.nlm.nih.gov/>. Accessed 9 February 2014.

National Oceanic and Atmospheric Administration (NOAA) National Weather Service (n.d.). UV Index: Annual time series. <http://www.cpc.ncep.noaa.gov/products/stratosphere/uv_index/uv_annual.shtml>. Accessed 1 January 2014.

New York State Department of Health (2013). NYS cancer registry and cancer statistics.

< http://www.health.ny.gov/statistics/cancer/registry/>. Accessed 14 March 2014.

North American Association of Central Cancer Registries (2012). Fast stats. <http://faststats.naaccr.org/selections.php?>. Accessed 14 March 2014.

Rivas, M., Rojas, E., and Calaf, G.M. (2012). Prediction of skin cancer occurrence by ultraviolet solar index. Oncology Letters 3, 893-896.

Rivas, M. (2013). Pers. comm.

Rogers, H.W., Weinstock, M.A., Harris, A.R., Hinckley, M.R., Feldman, S.R., Fleischer, A.B., and Coldiron, B.M. (2010). Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch. Dermatol. 146, 283-287.

Rosenberg, M. (n.d.). Geographic centers of the fifty states. <http://geography.about.com/library/weekly/aa120699a.htm>. Accessed 20 February 2014.

Skin Cancer Foundation (2013). Skin Cancer Facts. <http://www.skincancer.org/skin-cancer-information/skin-cancer-facts#men/women>. Accessed 20 February 2014.

Skin Cancer Foundation (n.d.). Understanding UVA and UVB. <http://www.skincancer.org/prevention/uva-and-uvb/understanding-uva-and-uvb>. Accessed 23 February 2014.

Stulberg, D.L., Crandell, B., and Fawcett, R.S. (2004). Diagnosis and treatment of basal cell and squamous cell carcinomas. <http://www.aafp.org/afp/2004/1015/p1481.html>. Accessed 23 February 2014.

University of California, Santa Barbara (n.d.). Sun angle and seasons. <http://www.geog.ucsb.edu/~joel/g110_w08/lecture_notes/sun_angle/sun_angle.html>. Accessed 25 March 2014.

University of Kansas Medical Center (2012). Kansas Cancer Registry. <http://www2.kumc.edu/kcr/zsearch.aspx>. Accessed 30 March 2014.

Uong, A., and Zon, L.I. (2010). Melanocytes in development and cancer. J. Cell. Physiol. 222, 38-41.

World Health Organization (n.d.). UV radiation. < http://www.who.int/uv/faq/whatisuv/en/index2.html>. Accessed 23 February 2014.

Weir, H.K., Marrett, L.D., Cokkinides, V., Barnholtz-Sloan, J., Patel, P., Tai, E., Jemal, A., Li, J., Kim, J., and Ekwueme, D.U. (2011). Melanoma in adolescents and young adults (ages 15 to 39 years): United States, 1999-2006. J. Am. Acad. Dermatol. 65, S38.e1-13.