UNIVERSITY OF CALIFORNIA,
IRVINE

# Adolescent and Young Adult Melanoma in California: The effect of access to care and race/ethnicity on incidence and survival.

THESIS

submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in Epidemiology

by

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Thesis Committee:
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# DEDICATION

To

My parents, Gary and Sylvia Bottom
For everything, I would not have made it this far without your love and support

My brother, Riley Bottom
For being such an inspiration in your academic endeavors

My family, friends and mentors
For showering me with positivity, love and amazing feedback

And most of all,
My husband, Tommy and our two babies
For your encouragement and never ending love

Thank you, I am filled with so much gratitude.

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# ABSTRACT OF THE THESIS

Adolescent and Young Adult Melanoma in California: The effect of race/ethnicity on incidence and survival

By

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Master of Science in Epidemiology

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Professor Dr. Hoda Anton-Culver, Chair

Adolescent and young adults who are diagnosed with cancer are known as the "missing" age group. Oncology research is usually focused on pediatric and adult cancers when the disturbing fact remains that eight times more adolescents and young adults (AYA) are diagnosed with cancer each year. In California, 70,000 AYAs are diagnosed with cancer each year and more research needs to be done to understand these cancers and provide better care for these patients. The influence of race, stage, insurance type and SES for AYA melanoma was examined in a large and racially diverse population from the California Cancer Registry from 1988-2009.

I found that an association between incidence risk of cancer and survival varied by race/ethnicity, insurance type and stage. Incidence was influenced most by age at diagnosis. Those patients with public insurance such as Medicaid had shorter survival times than those who had private insurance. Race/ethnicity, specifically Hispanics, had lower survival from melanoma as compared to the other race/ethnicities.

# Chapter 1: Introduction

## Cancer in Adolescents and Young Adults

Cancer is a disease in which mutated cells divide without any restriction and have the ability to spread and invade into surrounding tissues. It is a disease that can affect anyone and currently in the United States there are an estimated 13.7 million people that have had a previous cancer diagnosis, currently under cancer treatment or cancer free and about 1,665,540 new cancer cases are expected to be diagnosed in 2014 (1). Among these new 1.6 million new cases, 70,000 are expected to be adolescent and young adult patients. (2)

Adolescents and young adults with cancer fall into a category that is known as the "missing" age group in the oncology world. In the past special attention and focus for research had been focused on improving survival of adolescent and young adult (AYA) cancer but in the most recent decade the money and manpower has shifted towards research for childhood and adult cancer. The disturbing fact still remains that 8 times more adolescents and young adults are diagnosed with cancer each year compared to children and these AYA cancer patients also have a much higher mortality rate. Although the incidence and survival of cancer varies by many different factors it is overall the leading cause of death in AYA females, the second leading cause in AYA males and the leading cause of disease related death in all AYAs (3,5). This fact alone underscores the need to understand why there are disparities and find a better way to treat AYA patients.

**Race/ethnicity, socioeconomic status and AYA cancer**

The incidence and survival of all AYA cancers vary widely across race/ethnicity and socioeconomic status. In 2011, the National Cancer Institute found that "both cancer incidence and 5-year survival are highest among white AYAs." They also found that African Americans had intermediate incidence rates but the lowest survival, Asian/Pacific Islanders had the lowest incidence and fairly intermediate survival rates and Hispanics had intermediate incidence rates and intermediate survival rates. (see figure 1.1). Another important characteristic associated with AYA oncology is socioeconomic status. In 2014, McNally et all found that survival was worst in those AYAs with melanoma who lived in a more deprived socioeconomic areas. (6). This finding agrees with my hypothesis that race/ethnicity incidence/survival rates will be affected by the socioeconomic status of the patient. Socioeconomic status (SES) can be used as either a continuous or categorical variable. If used categorical, the patient will be classified into one of five categories: lowest, lower-middle, middle, higher-middle and highest SES based on quintiles of the YOSTSCL score. YOSTSCL is a measured index of SES level based on the principle components analysis of census variables. (7) SES is an important measure and can also be related to insurance coverage.

**Insurance status and AYA cancer**

Lack of insurance is one of the gaps in adolescent and young adult oncology that lacks sufficient research (8). It has been shown that those AYA patients who do not have insurance are more likely to be diagnosed at a later stage and therefore more likely to die from cancer. In 2014, Rosenberg et al used SEER data to collect 57,981 cases of AYA patients and reported that those patients that had no insurance had a 2.4

fold increased risk of being diagnosed with late stage disease than those insured patients. As one might expect, the authors report that those who were diagnosed with late stage disease had a 1.7 fold increased risk of mortality compared to those diagnosed with local stage disease (9).

**Melanoma in Adolescents and Young Adults**

**Pathophysiology**

Melanoma starts when the cells that make the pigment melanin called melanocytes suffer irrepairable DNA damage that causes them to multiply extremely quickly and transform into malignant tumors. Melanocytes are derived from neural crest cells on embryotic skin. These precursor cells are called melanoblasts and they proliferate and differentiate to the epidermis as melanocytes. Melanocytes are joined in the basal layer of the epidermis by keratinocytes. These are cells the major cell type that makes up the epidermis of a human. In the basal layer, keratinocytes go through the process of keratinization, which allows for the proliferation and differentiation of skin cells. Melanocytes, however, do not go through keratinization but instead stay in the basal layer and produce melanin for the skin. (10).

These two cells form melanin units when melanocytes spread their dendrites and connect with close by keratinocytes. These units consist of 1 melanocyte and 36 keratinocytes. The main purpose of the melanin unit is to produce melanin, which will absorb UV rays and protect the keratinocytes from the damage caused by UV. (11). The homeostasis of the epidermis is dependent on the interaction between these two types of cells. Keratinocytes are in charge of melanocyte proliferation and differentiation. (15). When melanocytes break free from the keratinocytes, they can proliferate rapidly and

spread. These rapidly growing melanocytes then cause nevi. Nevi are usually benign but sometimes these rapidly growing melanocytes develop a mutation that leads to melanoma. (12).

**Clinical Presentation and Staging**

When cancer metastasizes it usually can travel through the body in one of three ways. It can go through the blood, lymph system or tissue. When it moves through the blood, cancer cells get into the bloodstream and are able to metastasize to anywhere in your body. The same thing happens when they get into the lymph system. Lastly, when a cancer spreads through tissue it basically metastasizes to the closest nearby tissue (11).

According to the American Joint Committee on Cancer (AJCC 7th edition), there are five stages of malignant melanoma (13). Each stage of cancer has a primary tumor size, ulceration status, lymph node status and metastasis status. These five stages are (13):

Stage 0 (see figure 1.2)- also known as in situ and it occurs when the epidermis has abnormal melanocytes and these cells have the potential to become cancer

Stage I- divided in stage IA and IB (Local) (see figure 1.3)

IA: >1.0 mm tumor with zero ulceration, no lymph node involvement and no metastasis

IB: 1) >1.0 mm with ulceration, no lymph node involvement and no metastasis or 2) 1.01-2.0 mm with zero ulceration, no lymph node involvement and no metastasis

Stage II- divided into IIA, IIB and IIC (Regional) (see figure 1.4)

IIA: 1) 1.01-2.0 mm with ulceration, no lymph node involvement and no metastasis or 2) 2.01-4.0 mm with zero ulceration, no lymph node involvement and no metastasis

IIB: 1) 2.01-4.0 mm with ulceration, no lymph node involvement and no metastasis or 2) more than 4.0 mm with zero ulceration, no lymph node involvement and no metastasis
IIC: 1) more than 4.0 mm with ulceration, no lymph node involvement and no metastasis
Stage III (see figure 1.5)- in this stage, the tumor can be with or without ulceration and any thickness. The patient also usually has at least one of these characteristics: cancer spreads to one or more lymph node, lymph nodes may join together, cancer can spread to the closest lymph vessel and the lymph nodes, and small tumor may be found close to the original cancer site.
Stage IV (distant) (see figure 1.6)- the tumor can be any size, can be spread between 1 and more lymph nodes and can have metastasized to any other part of the body.

When cancer metastasizes it usually can travel through the body in one of three ways. It can go through the blood, lymph system or tissue. When it moves through the blood, cancer cells get into the bloodstream and are able to metastasize to anywhere in your body. The same thing happens when they get into the lymph system. Lastly, when a cancer spreads through tissue it basically metastasizes to the closest nearby tissue to it (10).

There are four most common histological types of cutaneous melanoma. Superficial spreading which accounts for about 70% of all melanomas and it usually starts as a benign mole that is found on the trunk, back and legs. Nodular melanoma accounts for about 15% of all melanomas and it is the most aggressive type. It usually begins as a mole or lesion that grows quickly and deeply. Acral Lentinginous Melanoma only accounts for about 5% of all melanomas. Even though it is only 5% of all melanomas, it accounts for about 50% of all melanomas diagnosed in patients who

are Asian, Hispanic and Black. It is hard to spot and often gets mistaken because it looks like a bruise under the nails or on the skin when it first develops. Lentigo Maligna Melanoma accounts for about 10% of all melanomas and it usually is mistaken for a sun spot in those who have experienced sun damage. (14).

**Epidemiology**

In the United States, malignant melanoma is the third most common cancer that is diagnosed in adolescents and young adults (15). According to Weir et al, a total of 361,394 cases of melanoma where diagnosed between 1999 and 2006 in the United States (4). The overall 5-year survival rate for adolescents and young adults with local malignant melanoma exceeds 90%. Local melanoma has a very good survival rate but it still counts for about 10% of all melanoma deaths in AYAs. The overall 5-year survival rate for regional melanoma is 65% and for distant melanoma it is 15%, which highlights the very aggressive nature of advanced melanoma and importance of prevention as well as early detection (15).

**Melanoma and Race/ethnicity**

In 2011, Weir et al used incidence data examined the trends of adolescent and young adult melanoma in the United States from 1999-2006 (4). They found that melanoma was higher in non-Hispanic whites than Hispanic, Black, American Indian/Alaskan Natives and Asian/Pacific Islander (see figure 1.7).

**Adolescent and Young Adult Melanoma in California**

**Epidemiology**

In California, the incidence of melanoma is the second most common cancer in adolescent and young adults under age 40 (2). About 260 AYAs are diagnosed with

melanoma each year and of all the melanoma deaths, about 5 to 10 % are adolescents and young people (2) (see figure 1.8).

**What is lacking?**

When reading through the literature, a lack of knowledge and research was noticed in the area of adolescent and young adult melanoma and even more there was a lack of papers exploring the disparities of their cancer incidence and outcome. It is important to understand the general demographics and statistics about adolescent and young adult oncology. By knowing where the disparities are, changes will be able to be made to make the treatment and survival of adolescent and young adult patients.

**Research Focus**

This project is aiming to improve knowledge of adolescent and young adult melanoma incidence and survival in California. This goal will be achieved by the following specific aims.

**Aim 1. Use the California Cancer Registry data to analyze cases of adolescents and young adults with melanoma in California (1988-2009).**

**Aim 1A. Determine demographic characteristics of melanoma cases and determine the effect of race on characteristics.**

**Aim 1B. Determine the melanoma risk by race/ethnicity and stage using multivariate logistic regression.**

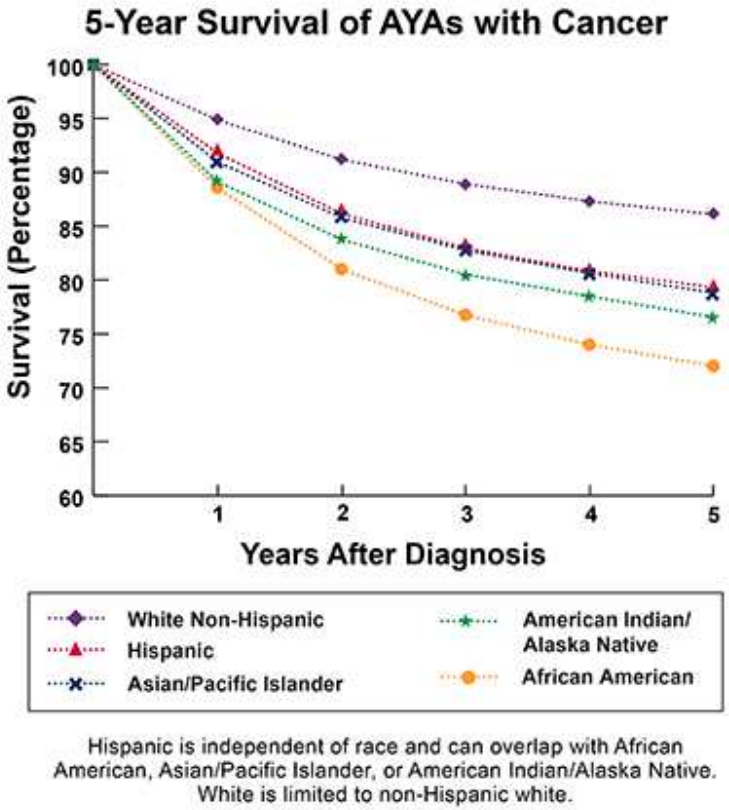
**Aim 2. Determine the incidence of AYA melanoma in California by age.**

**Aim 3. Determine survival of AYA melanoma in California by race/ethnicity using Kaplan-Meier Survival Curves and compare differences in overall survival and melanoma specific survival using Cox Proportional Hazard.**

By achieving these aims, more information will be known about adolescents and young adults with melanoma in California. Hopefully new information can bring to light the disparities these young adults face and real changes can be made to change the survival.

I will use the California Cancer Registry database (1988-2009) to perform a retrospective case-only analysis of malignant melanoma cases in adolescents and young adults. The data will be used to calculate the frequencies of patient characteristics and a univariate chi-squared test will be performed to determine if these characteristics vary by race/ethnicity. The variables that are positively associated from the univariate model will be included in a multivariate analysis to determine the melanoma risk by race/ethnicity. I will use this data to calculate age-specific incidence rates by race/ethnicity for ages 15-39 years old. A multivariate Kaplan-Meier survival curve will be calculated to determine overall survival and melanoma specific survival by race/ethnicity. Cox Proportional Hazard model to will be performed to determine the hazard ratio to see if there is a difference in survival by race/ethnicity.

**Figure 1.1**




Hispanic is independent of race and can overlap with African American, Asian/Pacific Islander, or American Indian/Alaska Native. White is limited to non-Hispanic white.

**Figure 1.2**

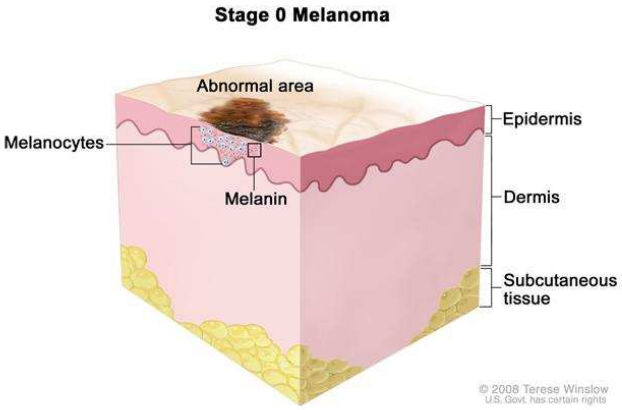


**Figure 1.3**

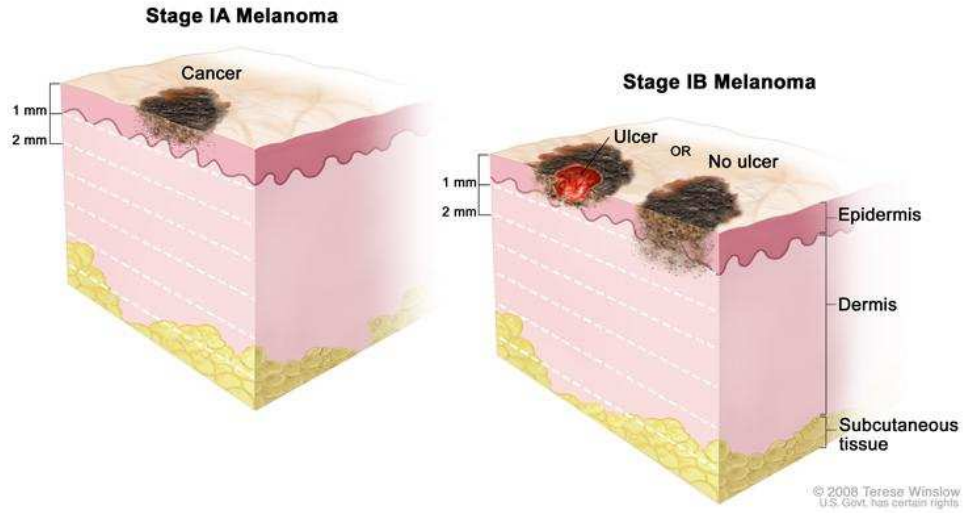
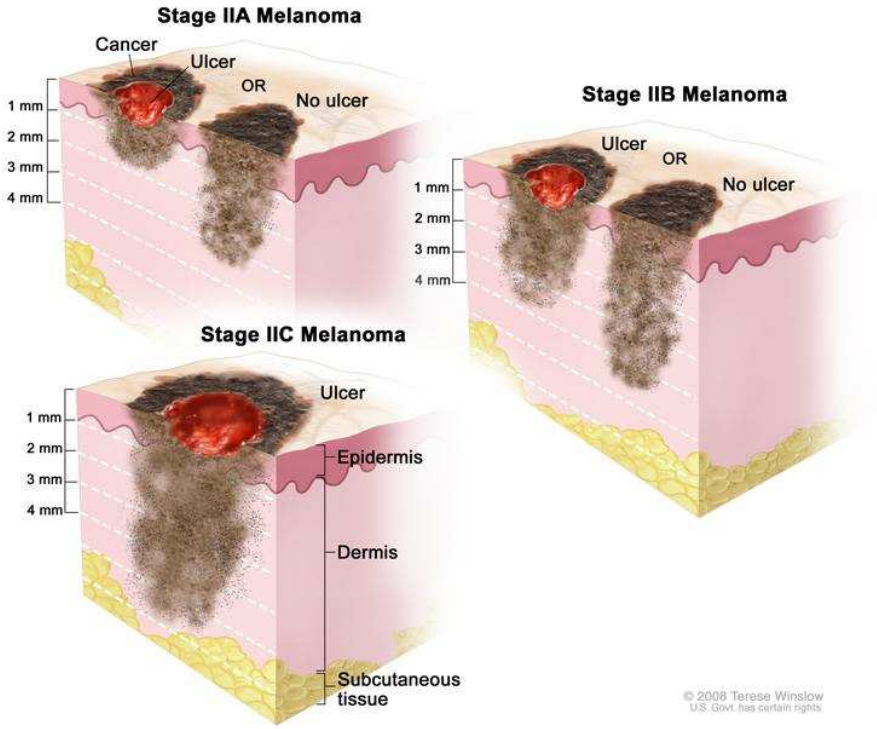
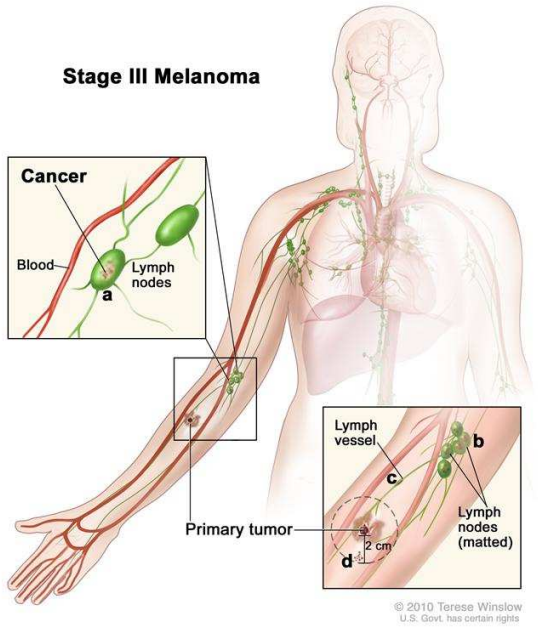



**Figure 1.4**



## Figure 1.5




## Figure 1.6

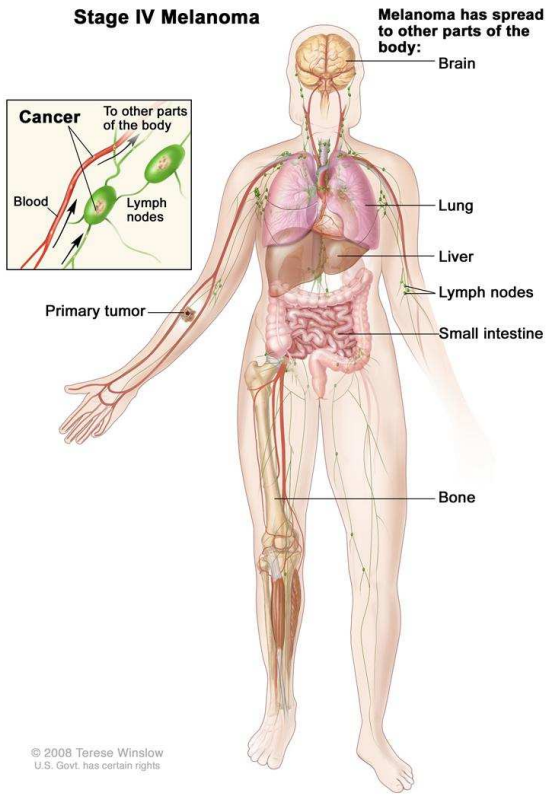


**Figure 1.7:** Bleyer, A., O'Leary, M., Barr, R., Ries, LAG (2006) Cancer Epidemiology in Older Adolescents and Young Adults 15-29 years of age. Including SEER Incidence and Survival: 1975-2000. National Cancer Institute, No. 06-5767.

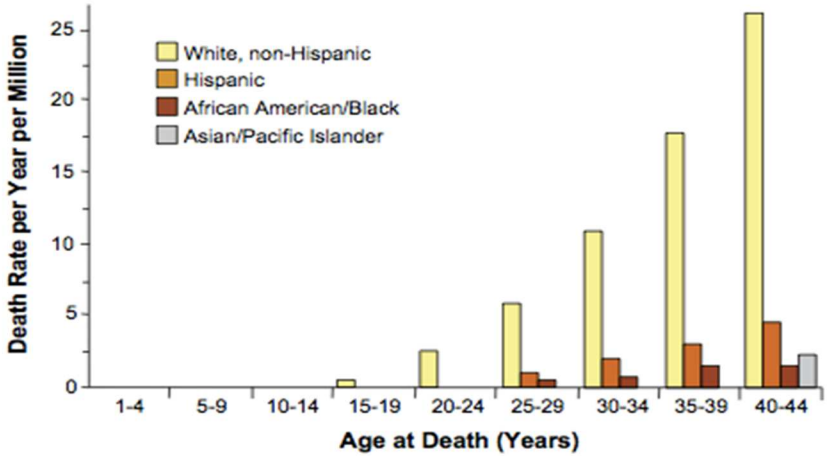
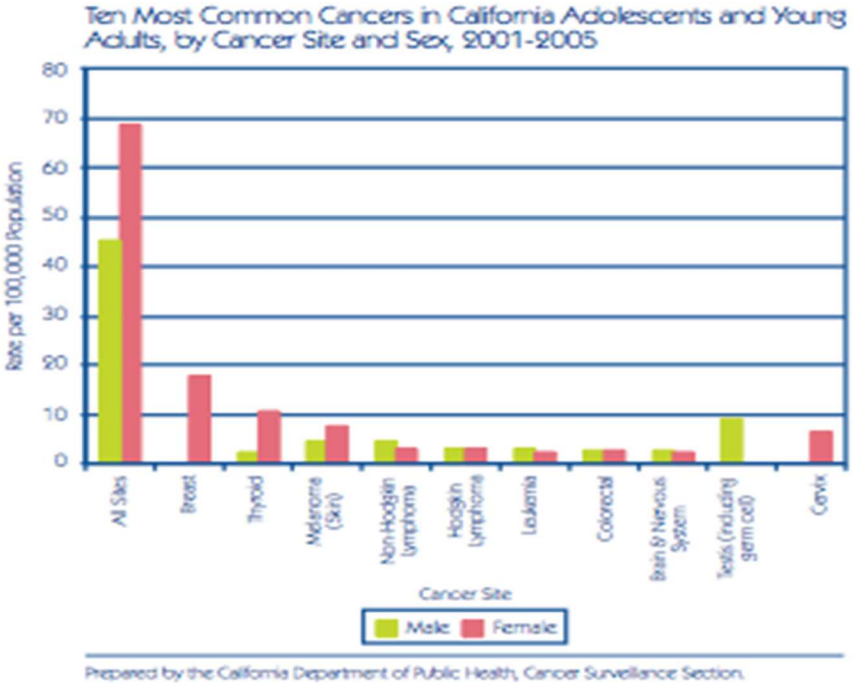



**Figure 1.8**



# Chapter 2: Methods

## Study Population

The California Cancer Registry is a population-based cancer surveillance system. The registry has counted cancer cases in California and collected descriptive tumor information since 1988. (15). This particular study will use the data found in the CCR to perform a retrospective case-only analysis of malignant melanoma survival found in adolescents and young adults in California.

All males and females between the ages of 15-39 diagnosed with malignant melanoma were included in the analysis. All first primary histologic types of cutaneous melanoma cases from 1988-2009 were collected from the CCR. Each type of histology has a certain ICD-O code but they all fall under the SEER site recode of melanoma (recode= 25010). The types of melanoma included are: Superficial Spreading Melanoma (SSM), Lentigo Maligna Melanoma (LMM), Nodular Melanoma (NM), Acral Lentinginous Melanoma (ALM), Melanoma Not Otherwise Specified (NOS) and all other malignancies. For the purpose of this study only invasive cases with behavior=3 (invasive) will be included.

## Race/Ethnicity Variable

In order to study the effect of race on survival from melanoma, the four major race/ethnicity groups seen most in California were included in the analysis. Non-Hispanic Whites (NHW), Non-Hispanic Black (NHB), Hispanics (H) and Asian Pacific Islanders (API). The CCR takes race/ethnicity from the medical records of patients and then the North American Association of Central Cancer Registries (NAACCR) Hispanic Identification Algorithm (NHIA) is used to determine Hispanic ethnicity. (17). The

algorithm takes into account the surname, maiden name, birthplace, and Hispanic origin and from there will classify the patient into the correct Hispanic group. For Asian/Pacific Islander patients, the NAACCR Asian/Pacific Islander Identification Algorithm (NAPIIA) took into account the gender, birthplace, first name and surname and from there classifies patients into the correct API group. Both of these algorithms are used to classify patients into the correct groups and helps to discourage misclassification of race.

**SES and Insurance Status Variable**

The socioeconomic status of the patients in the CCR was determined by using a method described in a paper by Yost et al. Since individual SES is not available in the CCR, census group block levels were used as a surrogate for individual SES. Data from the 1990 census was then used to create composite SES scores for each census block group. Seven variables (median school years, percentage of high school graduates, median income, percentage living below poverty level, median rent, median house value) were combined to create the score using a principal components analysis (7). This block group score, QUINYOST, ranges from 1 (low SES) to 5 (high SES) and is representative of the normal quintiles of the SES of the United States. For insurance, the variable of PAYER was used to determine if the patient has insurance and if so what type of insurance (private, Medicaid, Medicare, military, self pay or none).

**Behavior, Histology and Staging Variable**

The behavior of the tumor is taken from the medical records and it is a descriptive term that describes the pathology of the tumor. This variable is informative in knowing whether the tumor is benign, borderline, in situ or malignant. For the

purpose of this analysis, we will only be looking at malignant melanoma cases so all cases where behavior=3. The staging of melanoma is previously described in the introduction but basically the stages are: 0, IA, IB, IIA, IIB, IIC, III and IV. Histology describes the cell type of melanoma for the patients. It will help differentiate between superficial spreading, lentigo maligna, acral lentiginous, nodular and malignant melanoma not otherwise specified.

**Table 2.1 of ICD-O-3 codes for histological melanoma types**

| **Melanoma SEER site recode=25010** | |
|---|---|
| **Histology** | **ICD-O-3 code** |
| Superficial Spreading Melanoma (SSM) | 8743 |
| Lentigo Maligna Melanoma (LMM) | 8742 |
| Nodular Melanoma (NM) | 8721 |
| Acral Lentinginous Melanoma | 8744 |
| Melanoma Not Otherwise Specified (NOS) | 8720 |
| Other malignancies | 8722, 8723, 8730,8740, |
| | 8745,8761,8770-8773, |
| | 8780 |

**Exclusion Criteria**

For the purpose of this analysis, the following exclusion criterion was used. All cases diagnosed before age 15 and after age 39 were excluded since this analysis is only interested in adolescents and young adults. The four main racial/ethnic groups seen in California are included in this analysis and all other race/ethnicities (American Native and Other) were excluded. Only first primary malignant melanoma cases were included in analysis and all other tumors are excluded.

**Statistical Analysis**

All statistical analyses were conducted using SAS 9.2 statistical software (SAS Institute, Inc., Cary, NC). Statistical significance was established as a two-tailed p-value of less than 0.05.

**Aim 1: Collect melanoma cases from California Cancer Registry**

Cases were collected using the California Cancer Registry. Inclusion criteria is as follows: diagnosis year between 1988-2009, sex: male or female, race: Non-Hispanic Whites, Non-Hispanic Blacks, Hispanics and Asian/Pacific Islanders and first primary malignant tumors.

**Aim 1A: Determine demographic characteristics of melanoma cases and determine the effect of race on characteristics using univariate chi-square analysis.**

The frequencies of patient and demographic characteristics were calculated and presented in a table. A univariate chi-squared analysis was performed to determine which patient characteristics differ across race/ethnicity. These results were presented in a table. Statistical significance was set as p=0.5.

**Aim 1B: Determine the melanoma risk by stage of melanoma using multivariate logistic regression.**

A multivariate logistic regression model was performed to determine the risk of melanoma by stage of melanoma. The characteristics from Aim 1A that were positively associated with the outcome will be included in this model. The coefficients of the covariates and the odds ratios are reported in a table. Statistical significance was set as p=0.05.

**Aim 2. Determine the incidence of AYA melanoma in California by age.**

Age specific incidence rates were calculated for each age group (15-19, 20-24, 25-29, 30-34, 35-39) using the case counts and population at risk data from the CCR. These rates were then standardized using the 2000 US Standard Population Census data. The rates were not calculated for each year of age separately because the numbers were too small.

**Aim 3. Determine survival of AYA melanoma in California by race/ethnicity using Kaplan-Meier survival curves and compare differences in melanoma specific survival using Cox Proportional Hazard.**

To calculate the survival of AYAs with melanoma in California, Kaplan- Meier (KM) survival curves were calculated. KM curves determine the probability of surviving during a specific time. This type of analysis has three assumptions: 1) that patients who are censored have the same survival probability as those patients that continue, 2) that the survival probabilities are the same for all patients no matter when they were recruited for the study, 3) that the events happen at the time specified. The formula is as follows: (18).

$$S(t) = \frac{\text{Number of subjects living at the start} - \text{number of subjects died}}{\text{Number of subjects living at the start}}$$

To compare the differences in survival between race/ethnicities, the Cox Proportional Hazards model was used. A Cox model asses the relationship between the survival of a patient and characteristic variables of the patient population. It allows an estimate of effect of certain explanatory variables on survival. The general formula and equation is as follows: (19).

$$h(t) = \frac{\text{number of individuals experiencing an event in interval beginning at t}}{\text{(number of individuals surviving at time t) x (interval width)}}$$

# Chapter 3: Results

**Aim 1A: Determine demographic characteristics of melanoma cases and determine the effect of race on characteristics using univariate chi-square analysis.**

As shown in Table 3.1, significant differences were seen for the frequency of patient characteristics by race/ethnicity. The majority of late stage melanoma cases (stage 4) were found in Non-Hispanic Whites (81.5%) and Hispanics (14.8%). For all race/ethnicities, majority of the cases were diagnosed in early stage (stage 1). The age distribution for melanoma among races was found to be different for each race. In NH Whites, majority of the cases were diagnosed between the ages of 35-39 years. For Hispanics, more cases were diagnosed between ages 20-34 years. For NH Whites, more males were diagnosed than female (92.4% vs. 88.4%) and in Hispanics, more females were diagnosed than males (10.2% vs. 6.5%). In NH Whites, majority of the cases were Superficial Spreading Melanoma (SSM) (91.5%) and in Hispanics, majority of the cases were Acral Lentinginous Melanoma (ALM) (26.7%). Majority of NH Whites had no insurance or were self pay and for Hispanics the majority of cases had Medicaid. The last characteristic that was assessed was SES. In NH whites, majority of the cases were in the highest quintile (94.2%) and in the Hispanic population majority of the cases were in the lowest quintile (21.9%).

## Table 3.1 Patient Characteristics by Race/ethnicity

| Patient Characteristics | NH Whites | | NH Blacks | | Hispanics | | API | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| **Total n= 15337** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | |
| **Age** | | | | | | | | | <0.00 |
| 15-19 years | 543 | 89.90 | 4 | 0.66 | 48 | 7.95 | 9 | 1.49 | |
| 20-24 years | 1347 | 88.79 | 6 | 0.40 | 148 | 9.76 | 16 | 1.05 | |
| 25-29 years | 2560 | 89.57 | 7 | 0.24 | 262 | 9.17 | 29 | 1.01 | |
| 30-34 years | 3828 | 88.84 | 17 | 0.39 | 414 | 9.61 | 50 | 1.16 | |
| 35-39 years | 5538 | 91.55 | 19 | 0.31 | 449 | 7.42 | 43 | 0.71 | |
| **Sex** | | | | | | | | | <0.00 |
| Male | 5976 | 92.41 | 21 | 0.32 | 420 | 6.49 | 50 | 0.77 | |
| Female | 7840 | 88.39 | 32 | 0.36 | 901 | 10.16 | 97 | 1.09 | |
| **Stage** | | | | | | | | | <0.00 |
| 1A | 1753 | 89.90 | 2 | 0.10 | 176 | 9.03 | 19 | 0.97 | |
| 1B,2A,2B | 811 | 87.49 | 3 | 0.32 | 103 | 11.11 | 10 | 1.08 | |
| 3NOS,3A,3B,3C | 224 | 80.87 | 3 | 1.08 | 45 | 16.25 | 5 | 1.81 | |
| 4 | 88 | 81.48 | 1 | 0.93 | 16 | 14.81 | 3 | 2.78 | |
| **Histology** | | | | | | | | | <0.00 |
| SSM | 5424 | 91.48 | 12 | 0.20 | 450 | 7.59 | 43 | 0.73 | |
| LMM | 74 | 91.36 | 0 | 0.00 | 6 | 7.41 | 1 | 1.23 | |
| ALM | 59 | 58.42 | 4 | 3.96 | 27 | 26.73 | 11 | 10.89 | |
| NM | 825 | 86.57 | 4 | 0.42 | 110 | 11.54 | 14 | 1.47 | |
| DM | 149 | 85.63 | 1 | 0.57 | 17 | 9.77 | 7 | 4.02 | |
| Melanoma NOS | 6859 | 90.06 | 28 | 0.37 | 662 | 8.69 | 67 | 0.88 | |
| **Insurance** | | | | | | | | | <0.00 |
| Private | 8732 | 89.00 | 33 | 0.34 | 932 | 9.50 | 114 | 1.16 | |
| Medicaid | 106 | 88.33 | 1 | 0.83 | 13 | 10.83 | 0 | 0.00 | |
| Medicare | 23 | 88.46 | 0 | 0.00 | 3 | 11.54 | 0 | 0.00 | |
| None/Self pay | 54 | 94.74 | 0 | 0.00 | 2 | 3.51 | 1 | 1.75 | |
| Military/Other | 388 | 93.95 | 1 | 0.24 | 22 | 5.33 | 2 | 0.48 | |
| **QUINYOST** | | | | | | | | | <0.00 |
| 1st (low) Quintile | 925 | 76.01 | 14 | 1.15 | 266 | 21.86 | 12 | 0.99 | |
| 2nd Quintile | 1872 | 85.48 | 8 | 0.37 | 289 | 13.20 | 21 | 0.96 | |
| 3rd Quintile | 2837 | 89.81 | 13 | 0.41 | 288 | 9.12 | 21 | 0.66 | |
| 4th Quintile | 3963 | 92.29 | 14 | 0.33 | 276 | 6.43 | 41 | 0.95 | |
| 5th(high)Quintile | 4219 | 94.24 | 4 | 0.09 | 202 | 4.51 | 52 | 1.16 | |

**Aim 1B: Determine the melanoma risk by stage of melanoma using multivariate logistic regression.**

Patient characteristics were analyzed by stage of melanoma. The stages were divided by early stage (1 and 2) vs late stage (3 and 4). In all of the patient characteristics analyzed, majority of the cases were considered late stage as compared to early stage. Most late stage cases were aged 30-34 (0.71%) and most were male (0.69%). The majority of late stage cases were seen in NH Blacks but most early cases were diagnosed in Hispanics (0.36%). The late stage cases were more likely to be LMM (0.77%) whereas most early stage cases were ALM. This makes sense considering it was found that most Hispanics were diagnosed with ALM and Hispanics were the highest percentage found in the early stage cancer. Most patients were diagnosed with late stage cancer were in the low SES category (0.72%) whereas most patients diagnosed in early stage disease were in the high SES category (0.33%).

Multivariate logistic regression was performed to determine the odds of having late stage melanoma in all patient characteristics. It was found that NH Blacks had 43.4% increase in odds of developing late stage melanoma as compared to NH Whites but the results were not significant. Hispanics were less likely to develop late stage melanoma as compared to NH Whites (OR=0.92/ 95% CI: 0.80-1.04). Those patients that had no insurance or self pay had an increase in odds of late stage melanoma as compared to those patients with private insurance (OR=2.408/ 95% CI: 1.32-4.37). Those patients with Medicaid also had an increased risk of being diagnosed at late stage melanoma as compared to those with private insurance (OR=1.828/ 95% CI: 1.231-2.714). Those that were in the highest SES quintile were less likely to be

diagnosed with late stage melanoma as compared to those in the lowest SES quintile (OR=0.836/ 95% CI: 0.716-0.976).

### Table 3.2 Patient Characteristics by Stage of Melanoma

| Table of Characteristics by Stage | Early Stage | | Late Stage | | P-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Age** | | | | | <0.001 |
| 15-19 years | 185 | 0.31 | 419 | 0.69 | |
| 20-24 years | 530 | 0.35 | 987 | 0.65 | |
| 25-29 years | 887 | 0.31 | 1971 | 0.69 | |
| 30-34 years | 1263 | 0.29 | 3046 | 0.71 | |
| 35-39 years | 1959 | 0.32 | 4090 | 0.68 | |
| Total | 4824 | | 10513 | | |
| **Sex** | | | | | 0.03 |
| Male | 1974 | 0.31 | 4493 | 0.69 | |
| Female | 2850 | 0.32 | 6020 | 0.68 | |
| Total | 4824 | | 10513 | | |
| **Race/Ethnicity** | | | | | 0.01 |
| NH Whites | 4293 | 0.31 | 9523 | 0.69 | |
| NH Blacks | 13 | 0.25 | 40 | 0.75 | |
| Hispanics | 469 | 0.36 | 852 | 0.64 | |
| API | 49 | 0.33 | 98 | 0.67 | |
| Total | 4824 | | 10513 | | |
| **Histology** | | | | | <0.001 |
| SSM | 1734 | 0.29 | 4195 | 0.71 | |
| LMM | 19 | 0.23 | 62 | 0.77 | |
| ALM | 46 | 0.46 | 55 | 0.54 | |
| NM | 390 | 0.41 | 563 | 0.59 | |
| DM | 72 | 0.41 | 102 | 0.59 | |
| Melanoma NOS | 2374 | 0.31 | 5242 | 0.69 | |
| Other | 189 | 0.39 | 294 | 0.61 | |
| Total | 4824 | | 10513 | | |
| **Insurance** | | | | | <0.001 |
| Private | 4315 | 0.44 | 5496 | 0.56 | |
| Medicaid | 37 | 0.31 | 83 | 0.69 | |
| Medicare | 6 | 0.23 | 20 | 0.77 | |
| None/Self Pay | 15 | 0.26 | 42 | 0.74 | |
| Military/Other | 81 | 0.20 | 332 | 0.80 | |
| Unknown | 370 | 0.08 | 4538 | 0.92 | |
| Total | 4824 | | 10511 | | |
| **SES** | | | | | 0.01 |
| 1st (low) Quintile | 339 | 0.28 | 878 | 0.72 | |
| 2nd Quintile | 658 | 0.30 | 1532 | 0.70 | |

| | | | | |
|---|---|---|---|---|
| 3rd Quintile | 991 | 0.32 | 2168 | 0.68 |
| 4th Quintile | 1367 | 0.32 | 2927 | 0.68 |
| 5th (high) Quintile | 1469 | 0.33 | 3008 | 0.67 |
| Total | 4824 | | 10513 | |

## Table 3.3 Multivariate logistic regression

| **Multivariate Logistic Regression Analysis Modeling Late Stage Melanoma** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Coefficient** | | **Wald Chi-Squared** | | **Odds Ratio** | **OR 95% CI** | |
| | **Estimate** | **SE** | **Statistic** | **P-value** | **Estimate** | **Lower** | **Upper** |
| **Intercept** | 1.1742 | 0.1503 | 61.0248 | <0.0001 | . | . | . |
| Age | | | | | | | |
| 15-19 years (referent) | 1 | 1 | . | . | . | . | . |
| 20-24 years | -0.1725 | 0.052 | 11.0072 | 0.0009 | 0.685 | 0.552 | 0.85 |
| 25-29 years | -0.0281 | 0.0424 | 0.439 | 0.5076 | 0.791 | 0.647 | 0.968 |
| 30-34 years | 0.0496 | 0.0378 | 1.7204 | 0.1895 | 0.855 | 0.703 | 1.04 |
| 35-39 years | -0.0549 | 0.0344 | 2.5581 | 0.1097 | 0.77 | 0.636 | 0.933 |
| **Sex** | | | | | | | |
| Male (referent) | 1 | 1 | . | . | . | . | . |
| Female | -0.0289 | 0.0192 | 2.2685 | 0.132 | 0.944 | 0.875 | 1.018 |
| **Race** | | | | | | | |
| **NH White (referent)** | 1 | 1 | . | . | . | . | . |
| NH Black | 0.2382 | 0.2588 | 0.847 | 0.3574 | 1.434 | 0.737 | 2.792 |
| Hispanic | -0.2102 | 0.1074 | 3.8312 | 0.0503 | 0.916 | 0.804 | 1.043 |
| API | 0.0944 | 0.1634 | 0.3341 | 0.5633 | 1.242 | 0.862 | 1.79 |
| **Histology** | | | | | | | |
| **SMM (referent)** | 1 | 1 | . | . | . | . | . |
| LMM | 0.5272 | 0.2453 | 4.6168 | 0.0317 | 1.281 | 0.735 | 2.232 |
| ALM | -0.5063 | 0.1998 | 6.4185 | 0.0113 | 0.456 | 0.292 | 0.712 |
| NM | -0.4048 | 0.0868 | 21.7692 | <0.0001 | 0.504 | 0.431 | 0.591 |
| DM | -0.2347 | 0.155 | 2.2923 | 0.13 | 0.598 | 0.427 | 0.838 |
| NOS | 0.2999 | 0.0641 | 21.8978 | <0.0001 | 1.021 | 0.942 | 1.105 |
| Other | 0.0393 | 0.1032 | 0.1452 | 0.7032 | 0.786 | 0.641 | 0.964 |
| **Insurance** | | | | | | | |
| **Private (referent)** | 1 | 1 | . | . | . | . | . |
| Medicaid | -0.3821 | 0.1924 | 3.9453 | 0.047 | 1.828 | 1.231 | 2.714 |
| Medicare | -0.0126 | 0.3965 | 0.001 | 0.9747 | 2.645 | 1.053 | 6.645 |
| None/Self | -0.1065 | 0.2683 | 0.1576 | 0.6914 | 2.408 | 1.324 | 4.378 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Military/Other | 0.1849 | 0.1439 | 1.6516 | 0.1987 | 3.222 | 2.516 | 4.128 |
| Unknown | 1.3015 | 0.111 | 137.558 | <0.0001 | 9.843 | 8.78 | 11.034 |
| **SES QUINYOST** | | | | | | | |
| **SES: 1st Quintile (referent)** | 1 | 1 | . | . | . | . | . |
| SES: 2nd Quintile | 0.0139 | 0.0447 | 0.0968 | 0.7556 | 0.907 | 0.766 | 1.074 |
| SES: 3rd Quintile | -0.0276 | 0.0387 | 0.5082 | 0.4759 | 0.87 | 0.741 | 1.021 |
| SES: 4th Quintile | -0.0309 | 0.035 | 0.7775 | 0.3779 | 0.867 | 0.743 | 1.013 |
| SES: 5th Quintile | -0.0671 | 0.0347 | 3.7408 | 0.0531 | 0.836 | 0.716 | 0.976 |

**Aim 2. Determine the incidence of AYA melanoma in California by age.**

Age-specific incidence rates were calculated and the highest rate of 5.12 per 100,000 was found to be in the 35-39 year old category (IR=5.12/ 95% CI:-0.47 to 4.16). According to Table 3.4, incidence rates showed an increased for each age category. According to SEER data, the incidence rates in the older age groups also show the same sort of pattern. As age increases so does the incidence rate of melanoma.

**Table 3.4 Age-specific Incidence Rates**

**Age-Specific Incidence Rates per 100,000**

| | **Rate** | **95% Confidence Intervals** | |
|---|---|---|---|
| **Age** | | **Lower** | **Upper** |
| 15-19 years | 3.04132 | -0.08 | 0.66 |
| 20-24 years | 3.17763 | -0.32 | 1.95 |
| 25-29 years | 3.70455 | -0.42 | 2.37 |
| 30-34 years | 4.14603 | -0.3 | 2.57 |
| 35-39 years | 5.12377 | -0.47 | 4.16 |

**Aim 3. Determine survival of AYA melanoma in California by race/ethnicity using Kaplan-Meier survival curves and compare differences in melanoma specific survival using Cox Proportional Hazard.**

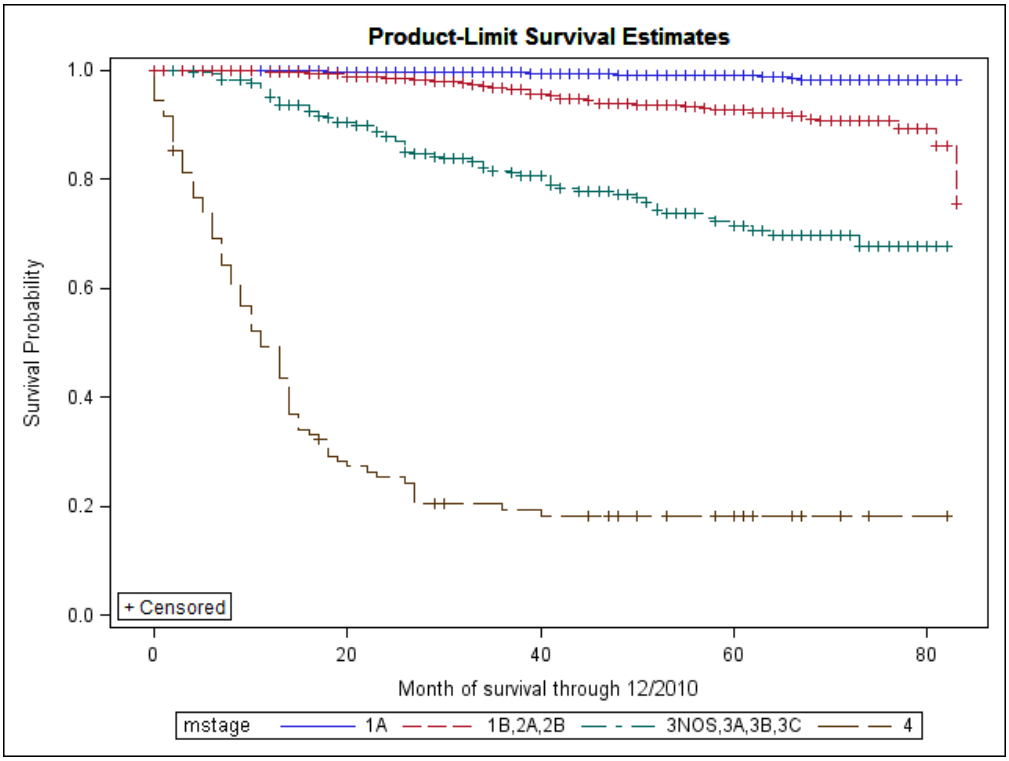
Kaplan-Meier curves were calculated for stage (Figure 3.1), race (Figure 3.2) and histology of melanoma (Figure 3.3).

For stage, significant differences in survival were seen among the different stages. The mean survival time among those with stage 1 cancer was 66.73 months as compared to those with stage 4 cancer whose survival time was 15.85 months.

For race/ethnicity, significant differences in survival were seen among the different race/ethnicities. The mean survival time for NH Whites: 235.63 months, NH Blacks: 160.09 months, Hispanics: 206.83 months and API: 134.08 months.

For histology, there were significant differences in survival by cancer cell type. The mean average of survival varied by months and cell type. The mean averages were as follows: ALM: 152.22 months, LMM: 119.72, NM: 173.60, Melanoma NOS: 227.08, SSM: 249.91, Spindle NOS: 172.09 and Unknown: 194.05.

## Figure 3.1 Kaplan-Meier curves by stage




## Figure 3.2 Kaplan-Meier Curves by race/ethnicity

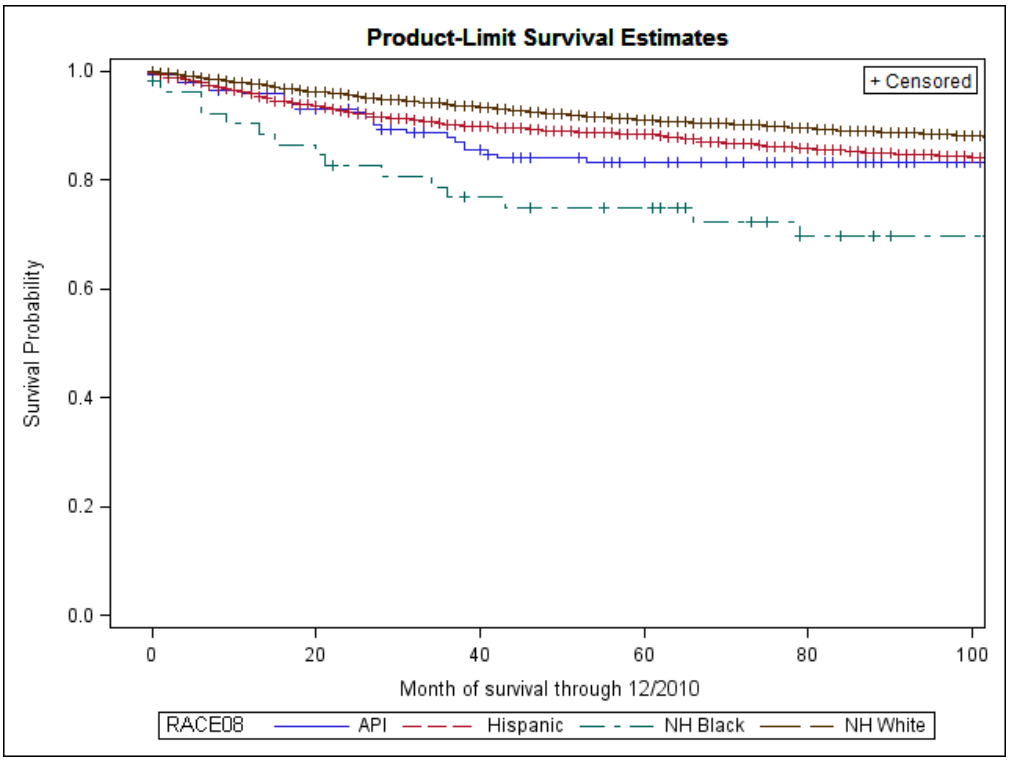
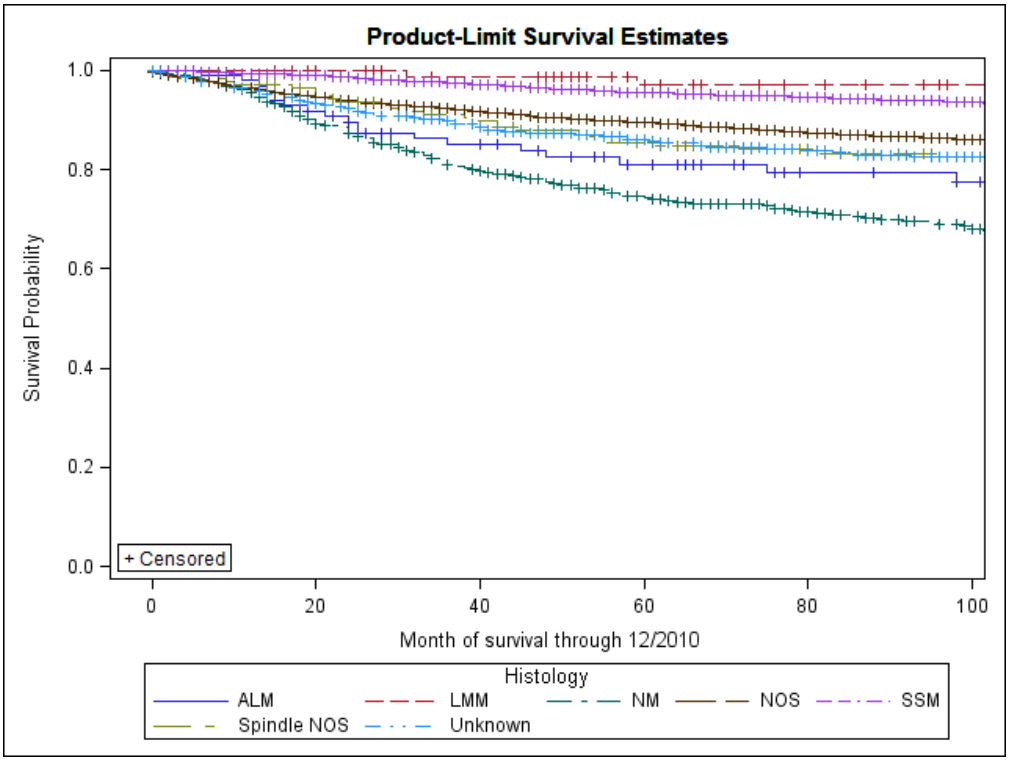


**Figure 3.3 Kaplan-Meier Curves by Histology**




A 5-year survival Cox Proportional Hazard model was made to calculate the differences in melanoma specific survival among race, stage and histology of disease. As seen in Table 3.5, patients that were diagnosed with stage 2 melanoma had a 6 times increased 5 year risk of dying from melanoma as compared to those with stage 1 cancer (HR=6.775). The trend that is seen is that as stage increases so does the risk of death from melanoma. (HR stage 3=28.97, HR stage 4= 268.43). The highest risk for stage was in those patients that were diagnosed in late stage melanoma, they had about a 270 times increased risk of dying as those in early stage melanoma. For race/ethnicity however, there is no visible trend but it is apparent that those patients who are Hispanic have a 8.5% increased 5-year risk of dying from melanoma as compared to NH Whites. Both API and NH Blacks had a decreased risk as compared

to NH Whites. Lastly, those patients who were diagnosed with LMM, had a 5.5 times increased risk of dying from melanoma as compared to those who were diagnosed with SSM. The other histologies all had increased risk of dying as compared to SSM other than those patients diagnosed with other melanoma (HR ALM=1.450, HR NM=1.650, HR DM=1.614, HR Melanoma NOS=1.188).

**Table 3.5 Five year Cox Proportional Model**

| 5 year Survival | Coefficient Estimate | Wald Chi-Squared Statistic | P-value | Hazard Ratio HR |
|---|---|---|---|---|
| **Stage** | | | | |
| 1(ref) | 1 | 1 | | |
| 2 | 1.913 | 41.374 | <0.0001 | 6.775 |
| 3 | 3.366 | 127.663 | <0.0001 | 28.977 |
| 4 | 5.592 | 357.709 | <0.0001 | 268.431 |
| **Race** | | | | |
| NH White (ref) | 1 | 1 | | |
| NH Black | -12.993 | 0.001 | 0.969 | 0 |
| Hispanic | 0.081 | 0.166 | 0.683 | 1.085 |
| API | 0.457 | 0.012 | 0.913 | 0.951 |
| **Histology** | | | | |
| SSM (ref) | 1 | 1 | | |
| LMM | 1.711 | 2.817 | 0.093 | 5.535 |
| ALM | 0.371 | 0.372 | 0.541 | 1.450 |
| NM | 0.500 | 0.724 | 0.054 | 1.650 |
| DM | 0.478 | 0.965 | 0.326 | 1.614 |
| Melanoma NOS | 0.172 | 0.656 | 0.418 | 1.188 |
| Other | -0.222 | 0.392 | 0.531 | 0.801 |

# Chapter 4: Discussion

## Summary of major findings

This research was done mainly to further explore and expand the knowledge of adolescent and young adult melanoma. With this in mind, specific aims were developed to determine the number of melanoma cases in AYAs in California, the frequencies and risk of melanoma by race and stage, the incidence of melanoma by age and the risk of dying from melanoma. A summary of the major findings from this study can be seen below:

-Patients with no insurance, self pay or Medicaid had increased odds of late stage disease compared to those with private insurance

-Those patients who were in the high SES quintile group were less likely to be diagnosed with late stage disease as compared to those patients in the lowest SES quintile

-Incidence rates increased with each year of age category and this increase coincides with incidence rate increases in the older adult age groups

-Those patients who were diagnosed at stage 2, 3, or 4 had an increased risk of dying as compared to those who were diagnosed at stage 1

-Hispanics had an increased risk of dying from melanoma as compared to NH Whites

## Insurance type

According to this study, patients who had no insurance, were self pay or on Medicaid were more likely to be diagnosed with late stage disease as compared to those patients with private insurance. This is consistent with a similar finding in the

paper from Rosenberg et al, which found that those AYAs diagnosed with late stage cancer was more likely to have non private insurance (9). It is known that patients who do not have insurance or are on Medicaid most of the time have a more difficult time getting in to see a doctor or get a referral to specialists, a more difficult time receiving adequate care and therefore usually have an increased risk of having late stage disease. In another paper from Robbins et al, it was shown that those patients who were uninsured were almost 2 times more likely to be diagnosed at late stage disease. They found that the effect of insurance status had a strong effect on those with melanoma and they think that this could change with better insurance because melanoma is a very detectable disease at early stage (20). In other words, there is no reason why so much melanoma is being diagnosed at late stage when it should be caught sooner but since these patients either did not have insurance, were self pay or Medicaid, they did not get diagnosed until late stage which in turn decreases the survival odds.

**Socioeconomic Status**

In this study, patients who were classified as high SES were less likely to be diagnosed at late stage disease as compared to those with low SES. This may also be associated with the fact that a lot of the patients who are in low SES are also patients with no insurance, self-pay or Medicaid. In a paper by Reyes-Ortiz et al, they found consistent results in that patients who were diagnosed at late stage melanoma were more likely to be those patients from the low SES category. They also found that these patients had a decreased melanoma specific survival as compared to their high SES counterparts (21).

**Incidence Rates by age**

Incidence rates in this study increased as age increased and this is consistent with findings from a paper by Weir et al. They found that as age increased in both males and females, the rate of cancer also increased (4). This sort of pattern is also seen in the older adult population. A conclusion can possibly be made that those older patients who are diagnosed are more likely to be exposed more often to melanoma risk factors such as lack of insurance, delay of diagnosis and possibly even things such as tanning beds or smoking.

**Stage of Melanoma**

In this research, patients who were diagnosed with late stage melanoma were more likely to die than those were diagnosed with early stage melanoma. These findings were consistent with findings also seen in a paper by Pennie et al. They found that those patients when diagnosed by a dermatologist, who were diagnosed with stage 1 or 2 melanoma had better survival times than those diagnosed with stage 3 or 4 disease. Even though they also specified the diagnosis by dermatologist, they still found the same results that early stage melanoma has better survival than those diagnosed with late stage (22).

**Race/ethnicity and survival**

In a paper from Wu et al, they found that patients who were of non White ethnicity were more likely to have decreased survival as compared to their NH White counterparts (23). Though this study did not yield those exact results, I did find that patients who were Hispanics had an increased risk of dying from melanoma than those who were NH White. This may be due to the fact that much of the AYA Hispanic

population has low income and a lack of insurance. In 2010, Pollitt et al wrote a paper that said that many Hispanic late stage melanoma cases were diagnosed in low SES incomes (24). This supports the idea that Hispanics are more likely to have a lack of private insurance and therefore more likely to have decreased survival from melanoma.

## Strengths and Limitations

### Strengths

This study has many strengths and limitations but the most important strength is that it highlights the need for more research to be done in the field of adolescent and young adult oncology specifically melanoma. It also shows some key areas that need to be addressed more.

Since the California Cancer Registry is a rather large population database, it allowed for collection of a large amount of AYA patients. This is a strength for the study because most of the time, AYA oncology patients are considered rare and not many cases are usually found. It helps that all patients diagnosed with cancer in California between 1988 to present are added to the database.

### Limitations

This current study is a retrospective population based study and therefore has limitations that are based on the data. As with any cancer registry study, there is a limitation in the fact that the SES level that is in the database is neighborhood based and not individual level. Even though individual level SES was not available, the variable available still provides an accurate estimate of the effect of SES on melanoma incidence and survival.

## Novel Findings

In this study investigating AYAs with melanoma in California, there were a couple novel discoveries seen from the data. These discoveries that were found can provide a basis for future work and allow for more hypotheses to becoming generated about AYA oncology issues.

The first discovery that was seen was that more Hispanic women than men were diagnosed with cancer as compared to NH Whites who had more males than females.

| | NH Whites | Hispanics |
|---|---|---|
| Sex | | |
| Male | 92.41% | 6.49% |
| Female | 88.39% | 10.16% |

This was interesting because according to SEER data, the opposite is true of adults who have melanoma. According to the data, males had higher frequencies of all stages of melanoma as compared to females. This may be because Hispanic women are more likely to have increased patterns of pregnancy. Women who are pregnant have more access to health care, which in turn would allow for the diagnosis of melanoma sooner than males who do not have access to medical care. In a report released from the CDC in 2012 (25), they found that Hispanic women, especially in the 20-29 year old age group, had high rates of pregnancy. They found that the Hispanic women pregnancy rate was about 60% higher than those in NH Whites. This fact may help explain the difference in frequencies by sex in Hispanics and NH Whites. It would be important to continue to study this difference and maybe explore the idea of pregnancy related to increased melanoma diagnosis.

The next discovery is that the type of insurance (private vs. public) affected the risk of being diagnosed with late stage melanoma.

| Insurance | | |
|---|---|---|
| Private | 1 | |
| Medicaid | 1.828 | pvalue=0.047 |

This is very interesting because melanoma is a cancer that does not have a standard of care for screening. For example breast cancer has very specific guidelines for screening and discrepancies have been seen in survival and incidence between private and public insurance. In a paper from Halpern et al, women who had public insurance (Medicaid) or no insurance were more likely to be diagnosed with advanced stage disease as compared to those women who had private insurance (26). This is a finding that is expected but when thinking of melanoma it is something to take note of. Insurance should not have such an effect on melanoma because there is no real screening guideline. A possible explanation for this could be that those who have better access to care (private insurance) are more likely to go to the doctor for other medical issues and therefore have more of an option of being diagnosed with melanoma as compared to those with public insurance. This finding is something that should be investigated further and more research should be done in the future to see if stage of melanoma at diagnosis is also affected by the histology and insurance by race.

The last novel discovery is that Lentigo Maligna Melanoma (LMM) had an especially high hazard ratio as compared to Superficial Spreading Melanoma (SSM).

| Histology | |
|---|---|
| SSM | HR=1 |
| LMM | HR=5.53 |

This is very peculiar because LLM histology is mostly seen in older adults since it usually manifests from sunspots and comes as a result of many years of accumulation of sun exposure. In 2015, UpToDate mentioned that the peak incidence of LMM is usually between 65 and 80 years old but that the incidence of LMM is increasing in younger age groups (27). It would be important to dig further into why LMM is increasing in the AYA group when it is normally considered an older person's cancer. It is possible that the increase in sun tanning and tanning beds could also be a reason for an increase in LMM in the AYA age group. Future research can be done to see whether the incidence of AYA LMM also coincides with tanning bed use or if there are other risk factors highly associated with that diagnosis.

# Chapter 5: Conclusions

In this study, I found that the frequency, incidence and survival of adolescent and young adult melanoma varied by many factors. The three biggest factors in whether an AYA would survive melanoma were race, stage of the cancer and insurance type. I found that late stage melanoma usually meant a shorter survival time. As seen in table 3.5, Hispanics were less likely to survive late stage melanoma as compared to the other races. In table 3.3, it was shown that patients with public insurance had an increased risk of being diagnosed with late stage melanoma than those who had private insurance. These discoveries are not necessarily novel but they should be taken very seriously. I believe that because of the finding of Hispanics having less survival, more research should be focused on this population in California. Since about 39% of the population is Hispanic and it is always expanding, I believe that we need to provide more targeted prevention campaigns about the risk of melanoma to this population and help to increase the survival from melanoma.

Insurance is another issue that needs to be addressed more. As seen in table 3.3, patients who had non-private insurance had an increased risk of being diagnosed with late stage melanoma. I believe that even though Medicaid provides free medical care, a lot of time the access to care is not that adequate. When a primary care doctor diagnoses a patient with melanoma, it usually takes some time before they get their referral to see a specialist. It is important to be aware that the sooner diagnosis and treatments happen, the better the survival. Melanoma is preventable and can be cured when diagnosed early and so it is important to make sure diagnosis happens sooner to decrease the risk of death from melanoma.

This study was important because it adds to the knowledge of adolescent and young adult cancer, which is still vastly understudied, compared to pediatric and adult cancers. This study provides an idea that much still needs to be done in this field. This paper provides a basis that more resources should be provided for AYA prevention, diagnosis, treatment and research to provide the best outcomes for the adolescent and young adult population.

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