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Incidence and Profile of Uveal Melanoma in the United States, 2001-2017

by

Andrew Wade Smith

A thesis

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To the Graduate Faculty:

The members of the committee appointed to examine the thesis of Andrew Wade Smith find it satisfactory and recommend that it be accepted.

Dr. Ryan Lindsay, Ph.D. MPH

Major Advisor

Dr. Irene van Woerden, Ph.D.

Committee Member

Susan S. Tavernier, PhD, APRN-CNS AOCN

Graduate Faculty Representative

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Incidence and Profile of Uveal Melanoma in the United States, 2001-2017

Thesis Abstract—Idaho State University

Purpose: Analyze the incidence and profile of uveal melanoma in the United States from 2001 - 2017 using the combined Surveillance, Epidemiology, and End Results (SEER) and National Program of Cancer Registries (NPCR) database.

Materials and Methods: Patient cases were identified using the International Classification of Disease (ICD) for Oncology codes C69.0-6,8,9, C44.0-9, and histology categorization codes 8720-8790/3. Statistical calculations and analyses were performed with the standard functions of the SEER*Stat software and statistical functions in Microsoft Excel.

Results: There were a total of 35,457 cases of uveal melanoma from 2001 - 2017. The mean age-adjusted incidence was 6.3 per million (95% CI 6.2-6.4) for uveal melanoma. The age-adjusted incidence rates for uveal melanoma between 2001 2017 appear to be decreasing with an annual percentage change of -0.4% ($p<0.05$, 95%CI: -0.8%-0.0%)

Conclusions: Between 2001 - 2017 there was a decrease in incidence rates for uveal melanoma, but more research and investigations are needed.

Key Words: Uveal, Ocular, Melanoma, Incidence, Epidemiology, Oncology, SEER, NPCR

INTRODUCTION

In the United States and world-wide, cancer is the second leading cause of death among adults (WHO 2021, CDC, 2021) and the fourth leading cause of death among children in the United States (Cunningham, 2018). There were an estimated 1.8 million new cases of invasive cancer in the United States in 2020 alone (ACS, 2020). From that estimate, about 606,520 Americans will have succumbed to this disease in 2020 (ACS, 2020). One of the most common types of cancer among both adults and children is melanoma. Between 2006 and 2015, rates of cutaneous melanoma rose from 200.1 to 229.1 case per million (Paulson, 2020). Melanoma is defined as cancer of the skin that develops when cells called melanocytes grow out of control (ACS, 2020). A small fraction, about 3-5%, of all melanomas are ocular melanomas that arise in part of the eye known as the uveal tract. (Kaliki, 2015). Uveal melanoma is the most common primary malignancy of the eye (Jager, 2020) and is classified as a rare disease as it is estimated to be diagnosed in about only 2,500 people in the United States each year. (NORD, 2018) Uveal is so rare that in the report, *2018 World Health Organization Classification of Cutaneous, Mucosal, and Uveal Melanoma* only mentions uveal as "Pathway IX. Uveal melanoma (not considered further in this review)" (Elder, 2018).

Problem statement and aims of this study:

Since uveal melanoma is a rare cancer, current research has only been able to study from a small sample size. With the combined SEER and NPCR database, we have access to a larger reported population, especially when combining years, which could improve estimates of

the current incidence rate of uveal melanoma and trend over time. Additionally, further investigation into demographics, including known social determinants of health, has yet to be completed for uveal melanoma. This paper looks at data extracted from the National Program of Cancer Registries and Surveillance, Epidemiology, and End Results SEER*Stat Database: NPCR and SEER Incidence – U.S. Cancer Statistics 2001-2017. Data collected will describe trends and incidence rates for uveal versus cutaneous melanomas, demographics of uveal, and the clinical presentation of uveal melanoma. The aims of this paper are below:

- Describe incidence rates and trend of uveal melanoma.
- Produce updated demographic profile of people with uveal melanoma up to 2017.
- Determine the clinical presentation of uveal melanoma.

As with all other types of cancer that are reported upon and published, it is a high priority to establish updated baseline data and build upon previous research for uveal melanoma. Rare cancers effect all types of Americans as well as those worldwide and have devastating effect of those diagnosed and their loved ones. This paper aims to provide the most up to date data from one of the largest samples sets to be reported for uveal melanoma. The incidence rates and trends reported should give a current picture of the incidence and profile of uveal melanoma than those in previously published papers.

I have worked in oncological clinical research for the past seven years and prior to that I worked in emergency medicine. Not being able to offer updated, effective, and innovative therapies to those suffering from rare cancers or even acute disorders is motivating to

investigate them further to better understand them. I am an advocate for preventative medicine and upstream thinking when it comes to healthcare as a system.

Literature review

The eye has a complex anatomy with multiple elements that allow the brain to comprehend vision and sight *(Figure 1).* The uveal tract of the eye is the pigmented layer of the eye that includes the iris, ciliary body, and the choroid (Chattopahdyay, 2016) *(Figure 2).* The terms *"Ocular", "Uveal",* and *"Choroid"* are often interchangeable when discussing this type of melanoma due to "*Uveal*" making up over 80% of all ocular melanomas (Kaliki, 2015, McLaughlin, 2005) and "*Choroid"* making up about 90-95% of uveal melanomas (Spagnolo, 2012, Kalirai, 2015). About 50% of all uveal melanoma cases end in metastatic disease (Ma, 2021). These metastatic lesions are most often found in the liver, lung, and bone with a 5-year survival rate of 84% for small tumors, 68% for medium tumors, and 47% for large tumors (Kaliki, 2015). The 10-year survival rate for all metastatic uveal melanoma is 50% (Kaliki, 2015, NORD, 2018). We can compare these rates to cutaneous melanoma which can have a 5-year survival rate as high as 99% for thin melanoma caught early or as low as 66% for melanoma with lymph node involvement and 27% for those presenting with distant metastasis (ASCO, 2021).

The etiology of uveal melanoma has been researched with the *National Organization of Rare Disorders* (NORD) providing a thorough overview (NORD, 2018). NORD is a patient advocacy organization dedicated to rare diseases through identification, treatment, and cure through education, advocacy, research, and patient services. The overall underlying cause of

uveal melanomas still unknown but there may be a multitude of risk factors that contribute to the cancer's genesis. Abnormal DNA, Light-colored eyes, skin and hair color (Chattopahdyay, 2016, Kalilki, 2017), and those easy to sunburn (Kalilki, 2017) have been identified as the primary risk factors. There are also anatomical abnormalities that could contribute to the development of uveal melanoma. These factors include an atypical & common cutaneous nevi, cutaneous freckles, and iris nevi. Nevi are areas of the tissue that are discolored or raised marks and growths. Of note, exposure to ultraviolet (UV) rays from the sun have been linked to development of cutaneous melanomas but research on UV rays as a risk factor to uveal melanoma is inconclusive (Chattopahdyay, 2016, Kalilki, 2017). There are currently no modifiable risk factors associated with the development of uveal melanoma and genetics involving uveal melanoma are not fully understood (NORD, 2018, 28, 29). This makes preventative measures and efforts rather difficult.

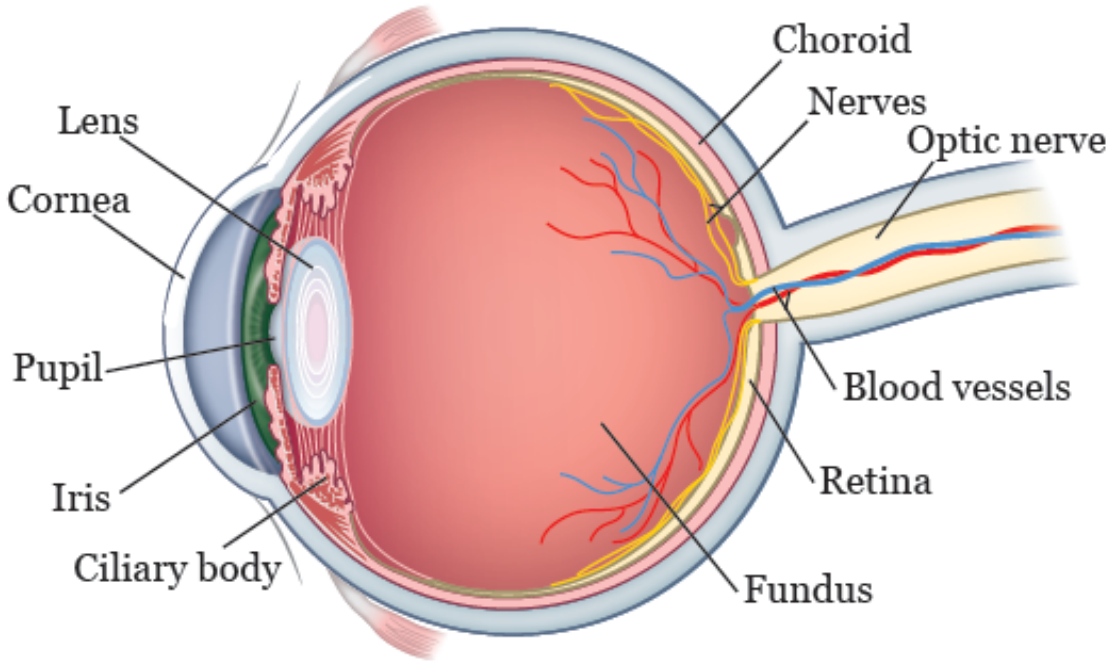

Figure 1: Ocular Anatomy
https://www.mskcc.org/cancer-care/patient-education/about-ocular-melanoma

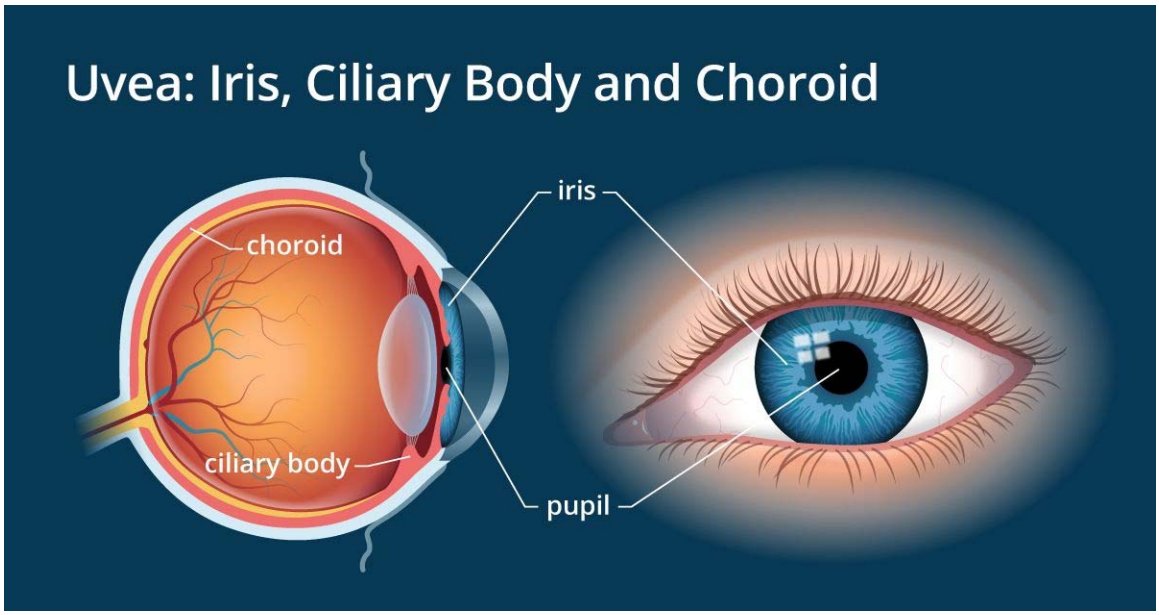

Figure 2: The Uveal Tract of the eye
https://www.allaboutvision.com/resources/uvea-iris-choroid.htm

In terms of genetic involvement, there are noted changes in specific genes in patients with uveal melanoma that may contribute to its formation. Abnormalities in chromosomes 1, 3, 6, and 8 have been shown to be common in uveal tumors. On top of those abnormalities there are few genes that may be responsible as well. Gene such as *BAP1, EIF1AX, SRSF2/SF3B1, MAPK, GNAQ, GNA11, PLCB4, and CYSLTR2* have all been shown to occur in greater frequency in uveal melanoma. (NORD, 2018, Chattopahdyay, 2016, Spagnolo, 2012, Kalirai, 2015, Ma, 2021, Frizziero, 2019, Kalilki, 2017, Field, 2014) Current research regarding these mutations and gene alterations is leading to better understanding of the cancer's molecular make up in hopes to lead to a better approach to treatment either through currently approved anticancer remedies such as chemotherapy, radiotherapy, surgery, and new targeted therapies.

Diagnosis of uveal melanoma is typically done via ophthalmologist or optometrist during a routine eye examination, often with the patient appearing asymptomatic (NORD, 2018). A patient may also present to in clinic complaining of eye problems such as vision issues or soreness (NORD, 2018) Confirmation of the disease is usually verified by the results of imaging, both radiographically and photographically, as well as pathologically from a biopsy via a qualified oncologist (Kalilki, 2017). Current treatments available fall into four categories; Surgery, radiotherapy, thermotherapy, and systemic/targeted/immune therapies.

Ophthalmic surgery is broken into two areas. Local resection is used to remove a portion of the affected area and enucleation (removal of the entire eye) is used if necessary, when the tumor is too large (Tarlan, 2016). Various forms of radiotherapy, specifically plaque radiotherapy, are also available for smaller, non-metastatic disease. Radiotherapy is most used

for tumors of the choroid in the back of the eye. The *Collaborative Ocular Melanomas Study (COMS)* however showed no difference in survival rates between radiotherapy and enucleation (removal of the eye) in medium sized tumors. (Weis, 2019)

Another therapy option for these types of tumor is transpupillary thermotherapy (TTT) and Photodynamic thermotherapy (PDT). (Weis, 2019) TTT is used for small choroidal tumors and is a noninvasive treatment using infrared light that increased the temperature of the tumor. PDT is similar by targeting the specific tumor but instead of a light to heat the tumor, it uses a photosensitizer that is injected intravenously. This chemical amasses in the tumor and then is activated by light causing tumor destruction by a direct cytotoxic effect.

The last forms of therapy for the treatment of uveal melanoma are systemic, immunotherapies, and targeted therapies. Traditional cytotoxic chemotherapies such as cisplatin, gemcitabine, and treosulfan (Spagnolo, 2012) have shown no influence on survival and have proven to not have any statistical significance for providing an increase in overall survival rate for uveal patients with metastatic disease. (Chattopahdyay, 2016) Uveal has proven to be highly resistant to these cytotoxic therapies and there is no therapeutic avenue to treat a patient with them. (Spagnolo, 2012)

Immunotherapies are treatments that assist the body's immune system to fight cancer. These biological therapies have been proven to be less toxic than traditional chemotherapies. In cutaneous melanoma, the immunotherapy *ipilimumab* has been studies extensively and thus it has been tried in uveal. An increase in overall survival has been shown in the few clinical trials.

(Chattopahdyay, 2016, Spagnolo, 2012) Other types of immunotherapies currently being studied in uveal melanoma include nivolumab and pembrolizumab which have been shown to increase overall survival in cutaneous melanomas that have been treated with ipilimumab. (Spagnolo, 2012)

Targeted therapies are treatments that target specific genes, mutations, or proteins. Since there have been several driver mutations found to be potentially associated with uveal melanoma it makes sense to utilize a targeted approach. Most recently, in February of 2021, the Food and Drug Administration granted "Breakthrough Therapy Designation" for the drug Tebentafusp (IMCgp100) for the treatment of unresectable or metastatic uveal melanoma. (Porter, 2021) this is the first novel treatment approval for uveal.

Chau et al discussed at the state of treatments for uveal at the 2019 Cure Ocular Melanoma Science meeting. The consensus is that due to the rarity of the cancer, more long term data is needed to increase sample size and more targeted and immunotherapy trials should be undertaken. Tumor size is still the primary factor affecting prognosis but with better genetic testing and advocating for preventative eye exams could augment the overall survival of those with uveal melanoma (Tarlan, 2016).

METHOD AND MATERIALS

Data about cancer incidence in this report come from the two federally funded population-based source of cancer cases in the United States, the Centers for Disease Control and Prevention's (CDC's) National Program of Cancer Registries (NPCR) dataset and the National

Cancer Institute's Surveillance, Epidemiology, and End Results Program dataset (CDC, 2021). Both the NPCR and SEER have reporting requirements for cases to be included (CDC, 2015). The combined NPCS and SEER dataset from 2001-2017 includes cancer incidence data from central cancer registries reported to NPCR in 46 states and the District of Columbia (CDC, 2021) and to SEER in 4 states which eliminates duplicate data. Data about all new diagnoses of cancer from patient records at medical facilities such as hospitals, physicians' offices, therapeutic radiation facilities, freestanding surgical centers, and pathology laboratories are reported to central cancer registries, which collate these data and additionally review state vital records to collect information about any cancer deaths that were not reported as cases. The central cancer registries use standardized data items and codes as documented by the North American Association of Central Cancer Registries. These data are submitted annually to CDC and NCI and combined into one dataset (CDC, 2021). This report includes new cases of primary invasive uveal and cutaneous melanoma (International Classification of Diseases for Oncology, Third Edition code [C69.0-6,8-9, and C44.0-9]) (CDC, 2021) diagnosed during [2001-2017]; restricted to histology codes [8720-9-8790/3]. (*Table 6)*

Measures

-Incidence rates were age-adjusted to the 2000 US standard population and annual percentage change (APC) in the incidence rate were calculated from 2001 – 2017 using the weighted least squares method (Neter, 1989) in the SEER*Stat software.

-Demographics included were biological sex, age, race/ethnicity, and year of diagnosis.

-Clinical manifestation looked at the ICD codes for uveal (C69.0-C69.9), laterality, and extent of disease at diagnosis.

-For comparing to cutaneous melanoma we identified cutaneous melanoma as those that fell under ICD codes C44.0-C44.9)

Statistics

Calculations and analysis were performed with the standard functions of the SEER*Stat Software. (SEER, 2021) Incidence patterns to compare the rates and frequencies of uveal melanoma versus cutaneous melanoma were performed using X^2 calculations in Microsoft Excel. Two-tailed *P* value for significance was set a prior at alpha level 0.05. Incidence rates were age-adjusted to the 2000 US Standard populations which included 19 age groups via Census P25-1130 (CDC, 2020, SEER, 2021, Paulson, 2020) to diminish any confounding by difference of age distribution over time. The methods of Tiwari et al 2006 were used to calculate 95% confidence intervals via the SEER*Stat software.

For this paper we choose the U.S. Data for 2001-2017 because this set of data was released in 2020 and has data points from both SEER and NPCR that include race and ethnicity, as well as population denominator that are sex-specific and race-specific (CDC, 2020).Access to this data base is public but a data use authorization form had to be submitted. Once approved a personalize username/password was provided. Trends and rates for incidence for the data pulled (2001-2017) were calculated using the 1-year averages with annual percentage change calculated by the weighted least squares method and age-adjusted to the 2000 US

standard population. Trends and rates were calculated as a standard function within the SEER*stat software (SEER, 2021) This study was deemed exempt by the IRB at Idaho State University (Appendix B),

RESULTS

There was a total of 35,457 uveal melanoma cases and 1,119,493 cutaneous melanoma cases returned from the database based on our search criteria of ICD disease and histology codes.

Incidence and trend of uveal melanoma

In previous research, mean age-adjusted incidence rates have been calculated at 5.2 per million from 1973-2013 by Aronow et al, 2018, 5 per millions by Kaliki et al 2014, and 5-6 per million by the NORD in 2018. The age-adjusted incidence rates for uveal and cutaneous melanoma by year of diagnosis were compared with uveal at cases per million and cutaneous at cases per 100,000. In 2001 the age-adjusted incidence rate was 6.4 per million for uveal melanoma and for cutaneous it was 17.0 per 100,000. The 2017 age-adjusted incidence rate for uveal melanoma was 5.7 per million and for cutaneous melanoma it was 22.3 per 100,000. The annual percent change (APC) for uveal was calculated to be statistically significate at a rate of -0.4 ($p<0.01$, 95% CI, -0.8% – 0.0%) (*Table 1)* for both genders combined. For cutaneous melanoma, the incidence rate showed an increase of 1.8% (95% CI, 1.6% – 2.1%) (*Table 2)*

Figure 3

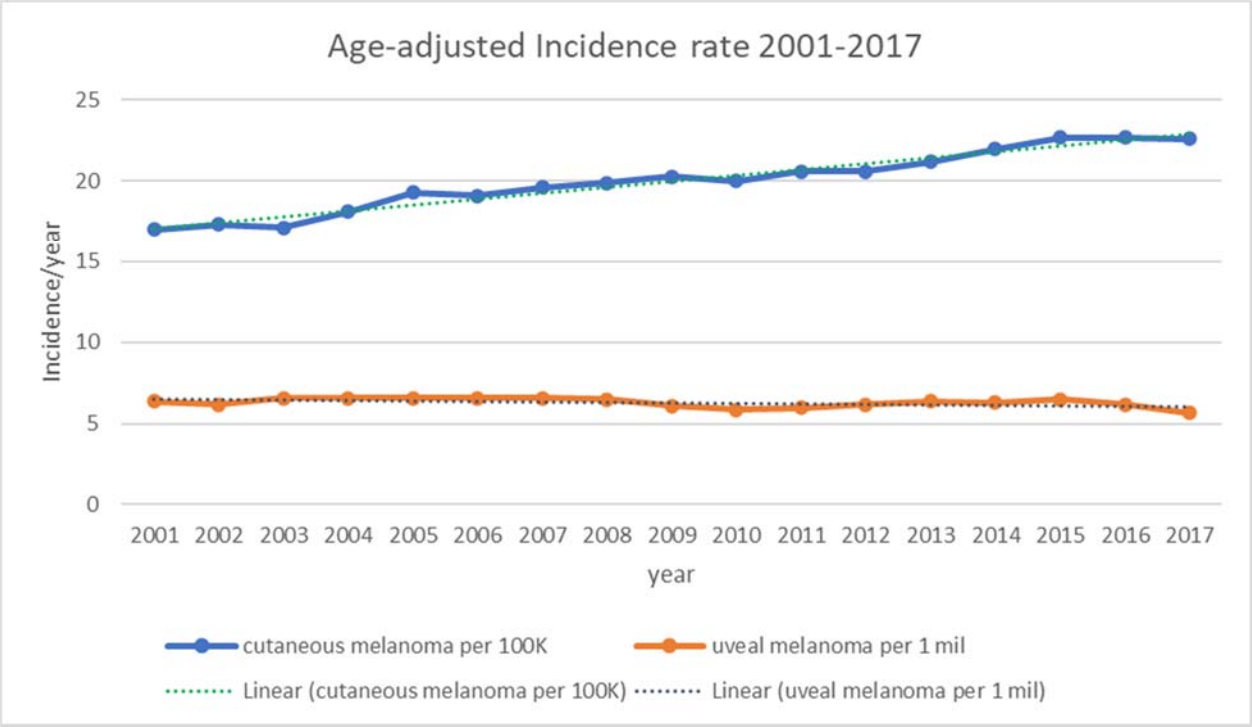

Figure 3: Age adjust Incidence Rates for Uveal (per 1Million) vs Cutaneous (per 100,000)

Demographic profile of people with uveal melanoma

Biological Sex

Of these uveal melanoma cases reported to SEER-NPCR between 2001 and 2017, there were 18,448 [52%] cases in males and 17,009 [48%] cases diagnosed in female. (*Table 3)* Among uveal melanoma cases, there were <16 cases for the age groups 00, 1-4, and 5-9 (include a percentage here). For adolescents and younger adults ages 10-14, 15-19, 20-24, 25-29, and 30-34 there were slightly more cases among females at (53.7%, 59.3%, 56.4%, 51.3%, 51.5%, respectively)]. From ages 35 onward, most cases were among males with 17,749 [52.2%] case between ages 35-85+. *(Table 4)*

Race

The racial breakdown of uveal melanoma shows it primarily effects Whites with 34,152 [96%] of the reported cases. The other races (Black, AIAN, API, other, and UNK) makes up the remaining 4% (n = 1,305). The gender breakdown between races was evenly spread with no defined group having a >52% split between genders. *(Table 5)*

Clinical presentation of uveal melanoma

Uveal cases were classified via ICD codes C69.0-9 which correspond with the primary tumor site. Most uveal tumors originate in the choroid (76%) followed in the distance by ciliary body (11%) and conjunctiva (6%). *(Table 6)* Laterality of the disease was compared and stayed consistent as well at an almost 50/50 split between right and left eye showing it does not favor one eye or the other. (*Table 7)*

The extent of the disease at diagnosis primarily shows uveal melanoma being diagnosed as "*Localized only"* with 27,716 [78.2%] cases between 2001 and 2017. The next highest is coded location is "*unknown*" at 4802 (14%) cases followed by "*regional direct extension only"* with 1907 (5%) of cases. Those cases mark "*unknown"* could be marks that way because the registrar entering data by not know any of the following: primary tumor site, tumor size, multiplicity (number of tumors), depth of invasion and extension to regional or distant tissues, involvement of regional lymph nodes, and distant metastases (CDC. 2020). When comparing extent of disease between uveal and cutaneous melanoma, there were statistically significant differences (p *<0.0001*) in every category besides "*localized only"* disease. The most

pronounced differences between extent of disease was "*Regional, regional lymph nodes only" was* 0.002% of uveal cases compared to 0.05% of cutaneous cases indicating that fewer cases of uveal are diagnosed via regional lymph nodes *(Table 8).* There was no significant difference between males and females when it comes to extent of disease. (*Table 10)*

The breakdown of diagnosed cases of uveal melanoma by geography is divided by state at diagnosis (*Table 12)* and by region (Northeast, Midwest, South, and West) (*Table 11).* There is no clinical significance between states and incidence of cases. There is however significance between incidence rates and regions. There is a clinically significant annual percentage change in the Northeast region (*Table 13*) at -1.8% ($p<0.01$, 95% CI, -2.9% - -0.7%) and a clinically significant annual percentage change in the Midwest *(Table 14)* at +0.7% ($p<0.01$, 95% CI, 0.1% - 1.4%). The rates for the South (*Table 15)* and the West (*Table 16)* were not clinically significant with a $P>0.001$ with rates of -0.6% and 0% respectively.

Age at Diagnosis

Regarding age at diagnosis for uveal melanomas, we see an increase in incidence among older age groups (*Figure 4). Approximately* 82% of all uveal cases are diagnosed in adults ages 50 and older *(Table 4).* Compared to cutaneous melanoma (*Table 9),(Figure 5)* cutaneous melanoma cases are diagnosed at earlier ages where uveal melanoma is diagnosed later (*p <00001)*. Figures 6 and 7 show the age-adjusted incidence rates for both uveal (*Figure 6)* and cutaneous *(Figure 7)*. What is shown is a steady curve for uveal melanoma for both males and females with males having a higher incident rate that females for age groups 35 and older.

Cutaneous melanoma echoes the results in Paulson's 2020 paper. Incidence rates for younger females is almost twice and high as young males but older males are almost three times as likely to develop cutaneous melanoma than females of the same age.

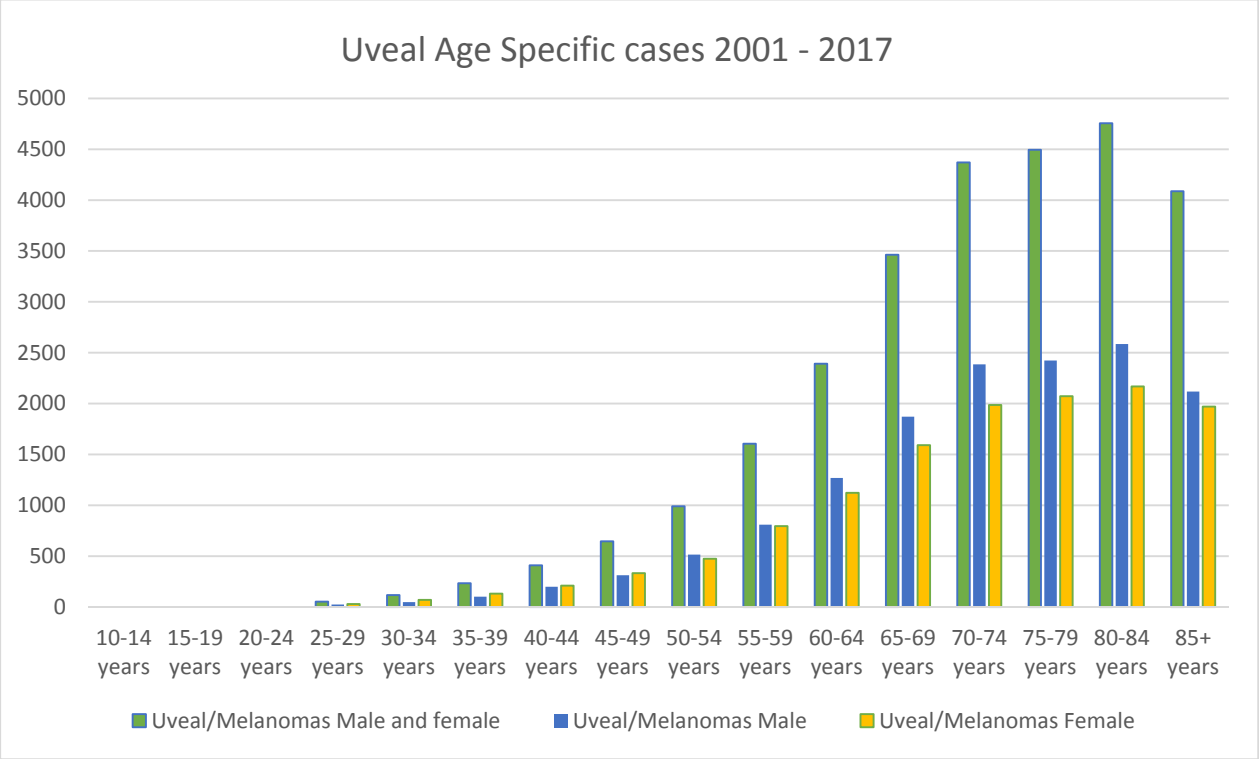

Figure 4: Uveal Incidence by age at diagnosis.

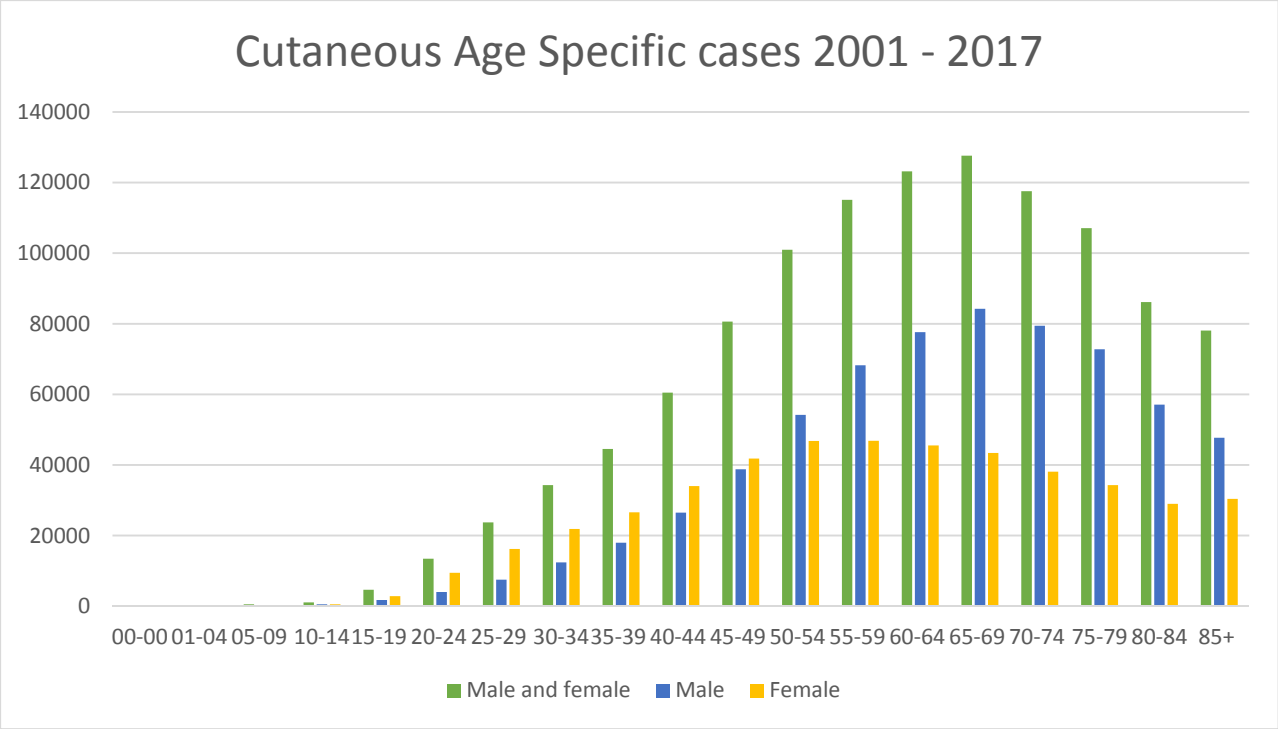

Figure 5: Cutaneous Incidence by age at diagnosis.

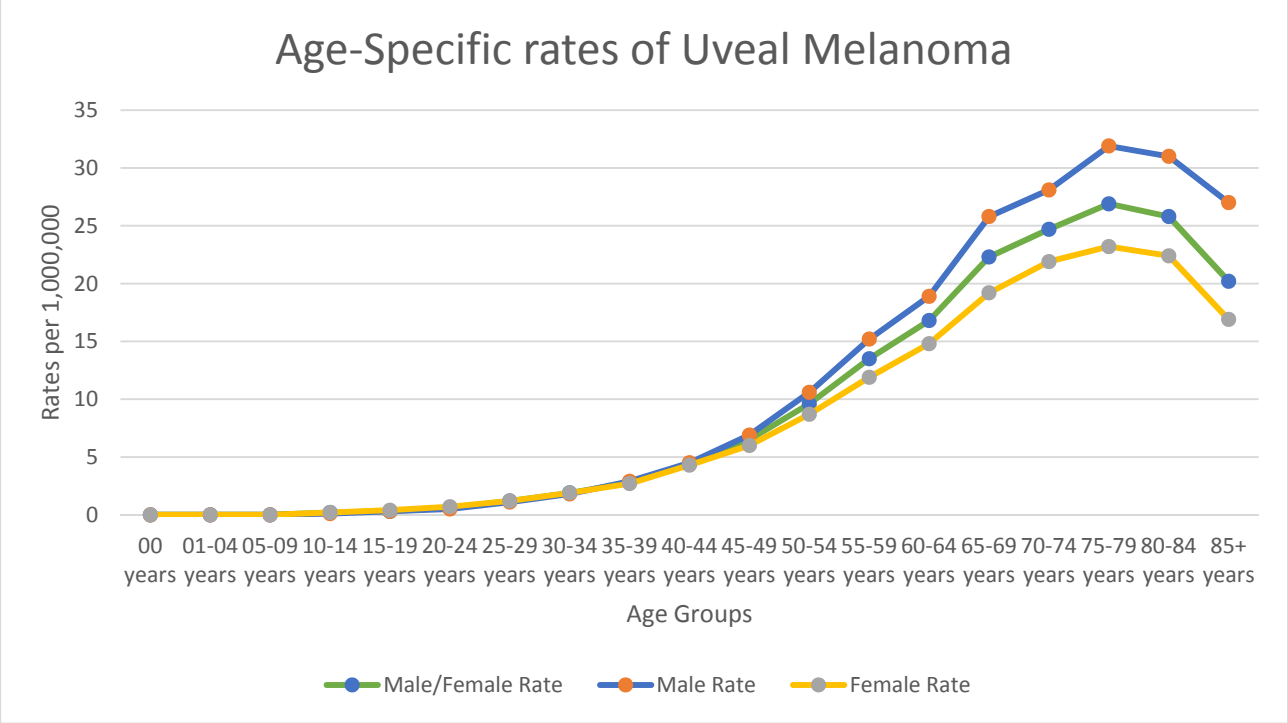

Figure 6: Age-Specific rates of uveal melanoma

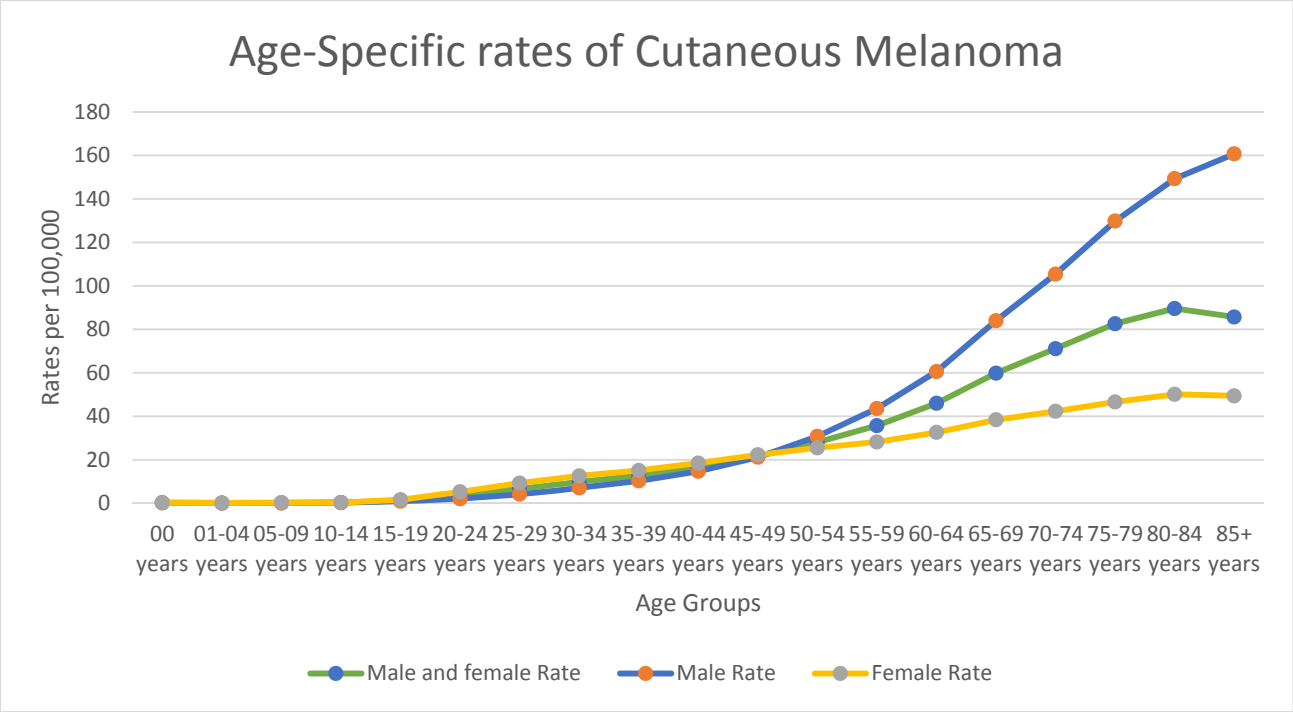

Figure7: Age Specific Rates of Cutaneious Melanoma

DISCUSSION

The combined information found in the Surveillance, Epidemiology, and End Results (SEER) and National Program of Cancer Registries (NPCR) database has provided the most up-to-date and comprehensive data for uveal melanoma. The total cases of uveal melanoma analyzed in our dataset (35,457 incidences) provided a much larger sample for analysis compared to a previous study that utilized cases from the SEER database only in 2018 (6,062 incidences from 1973-2013) (Aronow, 2018). The mean age-adjusted incidence of uveal melanoma from 1973-2013 was 5.2 per million population for the reported span of time, and while our study indicated an increased mean age-adjusted incidence rate (6.3 per million) for the range of 2001-2017, but, indicated a decreasing trend (-0.4 APC).

We compared the rate to that of the well-established data of cutaneous melanoma and noted a difference in incidence per year as cutaneous was on the rise at a 1.8% (95% CI, 1.6% - 2.1%) APC. Uveal does not appear to be detected or presented among younger people at the same rates as cutaneous melanoma due to uveal lack of environmental factors and its prevalence in older populations. In contrast to cutaneous melanoma, uveal does not appear to affect male versus females in the same way with males and females having a steady incidence rate for each age range. The spread of cases between anatomical sites was unremarkable when compared with past studies (Kalirai, 2015, Aronow, 2018, Kalilki, 2017). The extent of disease at diagnosis is also nonsignificant between genders with Males and Female getting diagnose at a similar rate.

There is a statistically significant annual percentage change for incidence rates in the Northeast region and Midwest region of the United States. In the Northeast, the rate is decreasing at a rate of -1.8% per 1,000,000 and for the Midwest the rate is increasing at 0.7% per 1,000,000 people. This could be in correlation with UV exposure, but the Northeast and Midwest of the United States occupy a very similar latitudinal coordinate.

Limitations and strengths

The national registry data is simply a high-level demographics snapshot and does not include information about UV light exposure, eye color, or sun-protective behavior. (26) Because of this we were not able to analyze potential relationships between certain risk factors, specifically modifiable ones, and uveal melanoma. Furthermore, the combined database only

had limited demographics variables that were not shared between the SEER database and NPCR database. Information not included in the data set is data regarding therapies, secondary malignancies, cause of death, therapy related to progression free survival and overall survival. In addition, aggregated and not individual data did not allow for assessment of relationships such as disparities in age of diagnosis by age, race, or gender, or multivariable statistics. However, the dataset utilized provided a large sample to estimate uveal melanoma incidence rates from 2001-2017 while adjusting for age. These data are comprehensive of detected uveal melanoma cases in the United States, but limitations to this study should be noted.

Conclusion

We have found and confirmed that uveal melanoma is rare cancer with decreasing incidence in the United States that affects older adults, those of White race, and male biological sex at higher rates than younger adults, those of other races, and females. Compared to cutaneous melanoma, the age-adjusted rates, factors associated with the etiology, and gender/age distribution are differ significantly. While cutaneous melanoma differs in incidences between gender and age and has established modifiable risk factors, the etiology for uveal melanoma remains inconclusive and the incidence rates remain stable between genders. There is still more data to be captured regarding modifiable risk factors for uveal melanoma. UV exposure should be investigated further since notable annual percent changes for incidence were note in two of the four regions of the United States.

While uveal melanoma is still a very rare cancer, more research regarding uveal melanoma should focus on what factors may account for the decreasing incidence. A decreasing incidence rate for a rare cancer is of interest because it may indicate that some sort of modifiable or environmental factor is changing. SEER and NPCR does not currently record data on therapies for primary or secondary treatment so we only speculate whether newer treatments for primary cancers are causing a decrease in incidence rates for those associated with being a secondary cancer. Trends in uveal melanomas, as well as studies that further explore risk and protective factors are warranted. Continued surveillance through the SEER and NPCR database should determine if the current downward trend continues in the United States and be compared with trends worldwide.

Appendix A: Tables

Year of Diagnosis						
Melanomas/Uveal						
	Male and female	Male and female	Male and female	Male and female	Male and female	Male and female
	Rate	SE	Lower CI	Upper CI	Count	Pop
Total APC	(-0.4)					
Total	6.3	0	6.2	6.4	35,457	5,193,974,513
	Uveal (per Mil)					
2001	6.4	0.2	6.1	6.7	1,791	282,115,961
2002	6.2	0.1	5.9	6.5	1,770	284,766,512
2003	6.6	0.2	6.3	6.9	1,948	290,107,933
2004	6.6	0.1	6.3	6.9	1,964	292,805,298
2005	6.6	0.1	6.3	6.9	2,008	295,516,599
2006	6.6	0.1	6.3	6.9	2,060	298,379,912
2007	6.6	0.1	6.3	6.9	2,083	301,231,207
2008	6.5	0.1	6.2	6.8	2,092	304,093,966
2009	6.1	0.1	5.8	6.4	2,003	306,771,529
2010	5.9	0.1	5.7	6.2	1,986	309,326,085
2011	6	0.1	5.7	6.3	2,058	311,580,009
2012	6.2	0.1	6	6.5	2,164	313,874,218
2013	6.4	0.1	6.2	6.7	2,289	316,057,727
2014	6.3	0.1	6	6.5	2,273	318,386,421
2015	6.5	0.1	6.2	6.8	2,401	320,742,673
2016	6.2	0.1	6	6.5	2,340	323,071,342
2017	5.7	0.1	5.5	6	2,227	325,147,121
	Rates are per 1,000,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard; Confidence intervals (Tiwari mod) are 95% for rates.					

Table 1: Year of Diagnosis Uveal Melanoma

Year of Diagnosis						
Cutaneous Melanoma						
	Rate	SE	Lower CI	Upper CI	Count	Pop
Total APC	1.8					
Total	20.2	0	20.2	20.2	1,119,493	5,193,974,513
	Cutaneous (per 100000)					
2001	17	0.1	16.8	17.1	47,781	282,115,961
2002	17.3	0.1	17.2	17.5	49,569	284,766,512
2003	17.1	0.1	17	17.3	50,127	290,107,933
2004	18.1	0.1	18	18.3	53,936	292,805,298
2005	19.3	0.1	19.2	19.5	58,464	295,516,599
2006	19.1	0.1	19	19.3	58,834	298,379,912
2007	19.6	0.1	19.4	19.7	61,319	301,231,207
2008	19.9	0.1	19.7	20	63,383	304,093,966
2009	20.3	0.1	20.1	20.4	65,712	306,771,529
2010	20	0.1	19.8	20.1	65,918	309,326,085
2011	20.6	0.1	20.4	20.7	69,106	311,580,009
2012	20.6	0.1	20.4	20.7	70,660	313,874,218
2013	21.2	0.1	21.1	21.4	74,226	316,057,727
2014	22	0.1	21.9	22.2	78,633	318,386,421
2015	22.7	0.1	22.5	22.9	82,447	320,742,673
2016	22.7	0.1	22.5	22.8	83,942	323,071,342
2017	22.6	0.1	22.5	22.8	85,436	325,147,121

Rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard; Confidence intervals are 95% for rates (Tiwari mod) and trends.

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

Table 2: Year of Diagnosis Uveal Melanoma

Biological Sex: uveal vs. Cutaneous				
Sex	**Uveal**	**%**	**Cutaneous**	**%**
Male	18,448	0.52	651,222	0.58
Female	17,009	0.48	468,271	0.42
Total	35,457	1.00	1,119,493	1.00

Table 3: Biological Sex

Age at Diagnosis						
Uveal/Melanomas						
	Male and female	%	Male	%	Female	%
00 years	<16		<16		<16	
01-04 years	<16		<16		<16	
05-09 years	<16		<16		<16	
10-14 years	54	0.00	25	0.46	29	0.54
15-19 years	118	0.00	48	0.41	70	0.59
20-24 years	234	0.01	102	0.44	132	0.56
25-29 years	411	0.01	200	0.49	211	0.51
30-34 years	646	0.02	313	0.48	333	0.52
35-39 years	991	0.03	516	0.52	475	0.48
40-44 years	1,605	0.05	809	0.50	796	0.50
45-49 years	2,392	0.07	1,269	0.53	1,123	0.47
50-54 years	3,463	0.10	1,872	0.54	1,591	0.46
55-59 years	4,371	0.12	2,385	0.55	1,986	0.45
60-64 years	4,495	0.13	2,423	0.54	2,072	0.46
65-69 years	4,755	0.13	2,586	0.54	2,169	0.46
70-74 years	4,088	0.12	2,118	0.52	1,970	0.48
75-79 years	3,493	0.10	1,786	0.51	1,707	0.49
80-84 years	2,480	0.07	1,184	0.48	1,296	0.52
85+ years	1,842	0.05	801	0.43	1,041	0.57

Table 4: Age at Diagnosis Uveal Melanoma

Race/Ethinicity (Uveal)	Male and female	M-F %	Male	%	Female	%
All races	35457	1.00	18448	0.52	17009	0.48
White	34152	0.96	17764	0.52	16388	0.48
Black	363	0.01	190	0.52	173	0.48
American Indian/ Alaska Native	105	0.00	51	0.49	54	0.51
Asian or Pacific Islander	257	0.01	126	0.49	131	0.51
Other unspecified (1991+)	97	0.00	53	0.55	44	0.45
Unknown	483	0.01	264	0.55	219	0.45

Table 5: Race/Ethnicity of Uveal Melanoma

Cutanious	*n*	%	Uveal	Frequency, *n*	%
C44.0-Skin of lip, NOS	1,800	0.16%	C69.0-Conjunctiva	2,062	5.82%
C44.1-Eyelid	3,899	0.35%	C69.1-Cornea, NOS	87	0.25%
C44.2-External ear	32,915	2.94%	C69.2-Retina	221	0.62%
C44.3-Skin other/unspec p	106,654	9.53%	C69.3-Choroid	26,799	75.58%
C44.4-Skin of scalp and ne	89,065	7.96%	C69.4-Ciliary body	3,882	10.95%
C44.5-Skin of trunk	362,401	32.37%	C69.5-Lacrimal glar	40	0.11%
C44.6-Skin of upper limb a	280,926	25.09%	C69.6-Orbit, NOS	385	1.09%
C44.7-Skin of lower limb a	190,683	17.03%	C69.8-Overlapping	395	1.11%
C44.8-Overlapping lesion c	1,119	0.10%	C69.9-Eye, NOS	1,586	4.47%
C44.9-Skin, NOS	50,031	4.47%	Total	35457	1.00
Total	1,119,493				

Table 6: Uveal and Cutaneous Melanoma Site and morphology 2001-2017

Laterality			
	Uveal	**%**	
Not a paired site	<16		
Right - origin of primary	17550	49%	
Left - origin of primary	17322	49%	
Only one side - side unspecified	90	0%	
Bilateral, single primary	19	0%	
Paired site: midline tumor	<16		
Paired site, but no information concerning	476	1%	
^	Statistic not displayed due to fewer than 16 cases.		

Table 7: Laterality of cancer origin

Extent of Disease		
	Uveal (%)	Cutaneous (%)
In situ	<16	<16
Localized only	27716 (78.2)	868129 (77.5)
Regional, direct extension only	1907 (5.4)	27928 (2.5)
Regional, regional lymph nodes only	74 (0.2)	57056 (5.1)
Regional, direct extension and regional lymph nodes	19 (0.05)	9701 (0.9)
Regional, NOS	27 (0.08)	6748 (0.6)
Distant site(s)/node(s) involved	912 (2.6)	50821 (4.5)
Not applicable	<16	<16
Unknown/unstaged/ unspecified/DCO	4802 (13.5)	99110 (8.8)
	35457 (100)	1119493 (100)

Table 8: Extent of disease

Age at Diagnosis						
cutaneous/Melanomas						
Age at Diagnosis	Male and female	%	Male	%	Female	%
00-00	168	0.00	86	0.51	82	0.49
01-04	260	0.00	122	0.47	138	0.53
05-09	519	0.00	237	0.46	282	0.54
10-14	1,086	0.00	547	0.50	539	0.50
15-19	4,637	0.00	1,778	0.38	2,859	0.62
20-24	13,460	0.01	4,004	0.30	9,456	0.70
25-29	23,730	0.02	7,509	0.32	16,221	0.68
30-34	34,286	0.03	12,411	0.36	21,875	0.64
35-39	44,555	0.04	17,964	0.40	26,591	0.60
40-44	60,491	0.05	26,486	0.44	34,005	0.56
45-49	80,608	0.07	38,779	0.48	41,829	0.52
50-54	100,976	0.09	54,187	0.54	46,789	0.46
55-59	115,110	0.10	68,251	0.59	46,859	0.41
60-64	123,152	0.11	77,608	0.63	45,544	0.37
65-69	127,619	0.11	84,222	0.66	43,397	0.34
70-74	117,528	0.10	79,444	0.68	38,084	0.32
75-79	107,089	0.10	72,781	0.68	34,308	0.32
80-84	86,124	0.08	57,111	0.66	29,013	0.34
85+	78,095	0.07	47,695	0.61	30,400	0.39

Table 9: Age at Diagnosis Cutaneous Melanoma

Melanomas/Uveal			
	Male and female	Male	Female
In situ	^	^	^
Localized only	27,716	14,395	13,321
Regional, direct extension only	1,907	1,036	871
Regional, regional lymph nodes only	74	40	34
Regional, direct extension and regional lymph nodes	19	^	^
Regional, NOS	27	^	^
Distant site(s)/node(s) involved	912	537	375
Not applicable	^	^	^
Unknown/unstaged/unspecified/DCO	4,802	2,414	2,388
^	Statistic not displayed due to fewer than 16 cases.		

Table 10: Extent of disease for uveal Melanoma, Males and Females

Melanomas/Uveal				
	Northeast	Midwest	South	West
Total	7,033	8,407	12,210	7,807
2001	410	415	582	384
2002	389	387	584	410
2003	450	469	648	381
2004	499	418	654	393
2005	436	482	674	416
2006	446	459	753	402
2007	443	463	740	437
2008	422	456	771	443
2009	347	519	682	455
2010	343	476	731	436
2011	361	499	742	456
2012	425	547	692	500
2013	427	607	710	545
2014	431	524	772	546
2015	457	561	866	517
2016	386	559	811	584
2017	361	566	798	502
^	Statistic not displayed due to fewer than 16 cases.			

Table 11: Uveal melanoma by US region

Melanomas/Uveal			
	Total		Total
Alaska	65	Mississippi	289
Alabama	555	Montana	182
Arkansas	279	North Carolina	1,175
Arizona	664	North Dakota	55
California	3,639	Nebraska	250
Colorado	669	New Hampshire	225
Connecticut	460	New Jersey	863
District of Columbia	23	New Mexico	160
Delaware	73	Nevada	219
Florida	2,621	New York	2,460
Georgia	859	Ohio	1,573
Hawaii	55	Oklahoma	413
Idaho	197	Oregon	694
Illinois	1,428	Pennsylvania	1,597
Indiana	819	Rhode Island	137
Iowa	568	South Carolina	446
Kansas	371	South Dakota	80
Kentucky	699	Tennessee	879
Louisiana	395	Texas	2,165
Massachusetts	947	Utah	296
Maryland	448	Virginia	590
Maine	252	Vermont	92
Michigan	1,091	Washington	895
Minnesota	528	Wisconsin	845
Missouri	799	West Virginia	301
		Wyoming	72
^	Statistic not displayed due to fewer than 16 cases.		

Table 12: Incidence of uveal melanoma by state.

Uveal/Melanomas					
		Rate/Trend	SE/P-Value	Lower CI	Upper CI
Northeast	Total PC	-28.8			
Northeast	Total APC	-1.8*	0	-2.9	-0.7
Northeast	2001 Rate	7.2	0.4	6.5	7.9
Northeast	2002 Rate	6.7	0.3	6.1	7.4
Northeast	2003 Rate	7.7	0.4	7	8.4
Northeast	2004 Rate	8.5	0.4	7.8	9.3
Northeast	2005 Rate	7.3	0.4	6.6	8
Northeast	2006 Rate	7.4	0.4	6.7	8.1
Northeast	2007 Rate	7.3	0.4	6.7	8.1
Northeast	2008 Rate	6.8	0.3	6.2	7.5
Northeast	2009 Rate	5.6	0.3	5	6.2
Northeast	2010 Rate	5.4	0.3	4.9	6
Northeast	2011 Rate	5.6	0.3	5	6.2
Northeast	2012 Rate	6.6	0.3	5.9	7.2
Northeast	2013 Rate	6.6	0.3	6	7.2
Northeast	2014 Rate	6.5	0.3	5.9	7.2
Northeast	2015 Rate	6.8	0.3	6.2	7.5
Northeast	2016 Rate	5.6	0.3	5.1	6.2
Northeast	2017 Rate	5.1	0.3	4.6	5.7

Table 13: Uveal incidence rates for the Northeast

Uveal/Melanomas					
		Rate/Trend	SE/P-Value	Lower CI	Upper CI
Midwest	Total PC	8.4			
Midwest	Total APC	0.7*	0	0.1	1.4
Midwest	2001 Rate	6.3	0.3	5.7	7
Midwest	2002 Rate	5.8	0.3	5.3	6.5
Midwest	2003 Rate	7	0.3	6.4	7.7
Midwest	2004 Rate	6.1	0.3	5.6	6.8
Midwest	2005 Rate	7.1	0.3	6.4	7.7
Midwest	2006 Rate	6.6	0.3	6	7.2
Midwest	2007 Rate	6.6	0.3	6	7.2
Midwest	2008 Rate	6.4	0.3	5.8	7
Midwest	2009 Rate	7	0	6.5	7.7
Midwest	2010 Rate	6	0.3	5.9	7.1
Midwest	2011 Rate	6.7	0.3	6.1	7.3
Midwest	2012 Rate	7.2	0.3	6.6	7.9
Midwest	2013 Rate	7.9	0.3	7.3	8.6
Midwest	2014 Rate	6.7	0.3	6.1	7.3
Midwest	2015 Rate	7.1	0.3	6.5	7.7
Midwest	2016 Rate	7	0	6.3	7.5
Midwest	2017 Rate	6.9	0.3	6.3	7.5

Table 14: Uveal incidence rates for the Midwest

Uveal/Melanomas					
		Rate/Trend	SE/P-Value	Lower CI	Upper CI
South	Total PC	-6.8			
South	Total APC	-0.6	0.1	-1.2	0
South	2001 Rate	5.9	0.2	5.4	6.4
South	2002 Rate	5.8	0.2	5.3	6.3
South	2003 Rate	6.1	0.2	5.7	6.6
South	2004 Rate	6	0.2	5.6	6.5
South	2005 Rate	6.1	0.2	5.6	6.5
South	2006 Rate	6.6	0.2	6.1	7.1
South	2007 Rate	6.4	0.2	6	6.9
South	2008 Rate	6.5	0.2	6	7
South	2009 Rate	5.7	0.2	5.2	6.1
South	2010 Rate	5.9	0.2	5.5	6.4
South	2011 Rate	5.8	0.2	5.4	6.2
South	2012 Rate	5.4	0.2	5	5.8
South	2013 Rate	5.3	0.2	4.9	5.7
South	2014 Rate	5.7	0.2	5.3	6.1
South	2015 Rate	6.2	0.2	5.8	6.7
South	2016 Rate	5.7	0.2	5.3	6.1
South	2017 Rate	5.5	0.2	5.1	5.9

Table 15: Uveal incidence rates for the South

Uveal/Melanomas					
		Rate/Trend	SE/P-Value	Lower CI	Upper CI
West	Total PC	-12.9			
West	Total APC	0	1	-0.6	0.6
West	2001 Rate	6.4	0.3	5.8	7.1
West	2002 Rate	6.8	0.3	6.1	7.5
West	2003 Rate	6.1	0.3	5.5	6.7
West	2004 Rate	6.1	0.3	5.5	6.8
West	2005 Rate	6.3	0.3	5.7	6.9
West	2006 Rate	6	0.3	5.4	6.6
West	2007 Rate	6.3	0.3	5.7	6.9
West	2008 Rate	6.3	0.3	5.8	7
West	2009 Rate	6.3	0.3	5.8	7
West	2010 Rate	5.9	0.3	5.3	6.5
West	2011 Rate	6.1	0.3	5.5	6.6
West	2012 Rate	6.4	0.3	5.9	7
West	2013 Rate	6.8	0.3	6.2	7.4
West	2014 Rate	6.6	0.3	6.1	7.2
West	2015 Rate	6.2	0.3	5.7	6.8
West	2016 Rate	6.8	0.3	6.3	7.4
West	2017 Rate	5.6	0.3	5.1	6.1
	Rates are per 1,000,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard; Confidence intervals are 95% for rates (Tiwari mod) and trends.				
	Percent changes were calculated using 1 year for each end point; APCs were calculated using weighted least squares method.				
~	Statistic could not be calculated.				
^	Statistic not displayed due to fewer than 16 cases.				
*	The APC is significantly different from zero (p<0.05). See P-Value in the APC row.				

Table 16: Uveal incidence rates for the West

Appendix B: IRB exemption

February 17, 2021

Andrew Smith
Community and Public Health
1311 E. Central Drive
Meridian, ID 83642

RE: Study NumberIRB-FY2021-166: Incidence of Uveal Melanoma in the United States

Dear Mr. Smith:

This message is your official notification that your project/survey IRB-FY2021-166: Incidence of Uveal Melanoma in the United States does not meet the definition of research under the Code of Federal Regulations Title 45 Part 46.102(d); therefore is not subject to review by the Institutional Review Board. You are free to conduct your study as submitted.

Sincerely,

Ralph Baergen, PhD, MPH, CIP
Human Subjects Chair

Appendix C: References

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