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Trends in Mortality of Adults with Melanoma in the United States SEER Population

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TRENDS IN MORTALITY OF ADULTS WITH MELANOMA IN THE UNITED STATES
SEER POPULATION

A Master's Thesis Presented

BY

DAWN TRUONG, AB

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April 7, 2022

BIOMEDICAL SCIENCES
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The Master's Thesis Committee has given
approval as to style and content of the Thesis

Sharina Person, PhD, Chair of Committee

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The signature of the Dean of the Morningside Graduate School of Biomedical Sciences signifies
that the student has met all master's degree graduation requirements of the school.

Dean of the Morningside Graduate School of Biomedical Sciences

Program

Master of Science in Clinical Investigation

April 7, 2022

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ABSTRACT

Background: While death from melanoma of the skin has been gradually decreasing over the past few decades, melanoma continues to be the leading causes of death among skin cancers. Less is known about specific causes of mortality among patients with melanoma and how or whether trends in cause of death among patients diagnosed with melanoma have changed in recent years.

Objective: To examine temporal trends in the cause-specific mortality among adult patients diagnosed with melanoma in the US between 2000-2013.

Methods: US patients ≥ 45 years when diagnosed with melanoma were identified using data from the Surveillance, Epidemiology, and End Results Program, 18 Registries (SEER-18). Joinpoint regression analysis was used to examine the trends in cause-specific mortality among patients who were diagnosed with melanoma and died from either melanoma or other causes of death. Trends were also examined separately by age, sex, and geographic region.

Results: A total of 52,675 patients diagnosed with melanoma who died from either melanoma or other cause of death (median age 74 years, 67% male) were included in the analysis. Overall, 31% of deaths were due to melanoma specifically, whereas 69% died from various other causes. A marked decline in melanoma-specific mortality was observed overall and across strata by age, sex, and region in the US beginning around 2013-2014. Among all causes of death, 55% were due to melanoma within 1 year after diagnosis and declined to 25% over the course of 6 years. A marked decline of at least 2.5% in mortality per year from other causes was observed among females, males, those 65 – 74 years or 75 years and older, and those living in northeastern, midwestern, western, and southern regions of US who were diagnosed with melanoma.

Conclusions: Changes in cause-specific mortality rate among patients with melanoma were observed overall and across different subgroups. Our findings show that, among those diagnosed

with melanoma, the risk of melanoma-specific death is decreasing within the last two decades, and that the deaths among those with melanoma are more likely to be from other causes such as heart disease, lung cancer, and other conditions. Future studies are needed to assess the trends in melanoma mortality as treatments and diagnostic methods continue to advance.

Keywords: Melanoma, cause-specific mortality, melanoma-specific mortality

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LIST OF SYMBOLS, ABBREVIATIONS, OR NOMENCLATURE

APC: Annual percent change

SEER-18: Surveillance, Epidemiology and End Results Program, 18 Registries

UV: ultraviolet

PREFACE

As the largest organ in the human body, skin protects against injury, regulates body temperature, preserves moisture, and functions in other essential capacities. Over the last few decades, the incidence of skin cancer in the United States has been on the rise. In fact, melanoma, a cancer of the pigment cells of the skin, is the most common cause of skin cancer mortality. While national cancer registries have captured individual-level data on patients with melanoma for multiple decades, examination of mortality trends remains an area of continued research. To the best of our knowledge, there have been no previous studies examining temporal trends in melanoma and non-melanoma causes of death within the SEER-18 population. We analyzed the mortality trends among patients with melanoma to elucidate areas for potential enhancement of care and shed light on whether patients with melanoma are dying from the disease itself or other competing causes.

CHAPTER 1: INTRODUCTION

Over the past few decades, melanoma of the skin has continued to rise in incidence and remains the leading cause of death among skin cancers in the United States, accounting for 5.6% of all new cancers and 1.2% of all cancer deaths. In 2021, there were 106,110 new cases of melanoma and 7,180 deaths [1]. Risk factors for melanoma include ultraviolet (UV) ray exposure, moles, family history of melanoma, older age, white race, and fair skin; before 50 years of age, females have higher rates of melanoma than males, while males have higher rates thereafter [2].

Despite an increasing incidence of melanoma in the U.S., death rates are declining faster for this cancer than they are for other common cancers. The decrease in melanoma deaths has been attributed to the introduction and approval of new therapies, such as targeted and immune checkpoint inhibitors in 2011 by the US Food and Drug Administration [3]. Subsequently, melanoma mortality has decreased by 5-7% annually between 2014 – 2018 [4]. However, these data may be misleading when further examining melanoma mortality among population subgroups. For example, after controlling for stage, site at diagnosis, and other characteristics, black patients fared worse than white patients in melanoma associated mortality, even though their lifetime risk of diagnosis is 26 times lower [5]. Overall, the 5-year survival rate associated with melanoma has steadily increased, from 90% in 2000 to 93% in 2013. However, the 5-year survival rate is lower and continues to decrease for black as compared with white patients. A similar trend is seen among sex-specific 5-year survival rates, with females (93% in 2000 to 95% in 2013) faring better than males (88% in 2000 to 91% in 2013) [6].

Given the overall improvement in survival among males and females with melanoma during recent years, it is likely that causes of death other than melanoma will be progressively more common. We also hypothesized that with increased time since the primary diagnosis of

melanoma, patients will be less likely to die from melanoma than from other causes of death. Additionally, we expected to see higher rates of melanoma mortality in males as compared to females, in patients diagnosed at older ages, and in those living in areas with a higher average UV index year-around.

CHAPTER II: METHODS

Study Population

We conducted a secondary analysis of the Surveillance, Epidemiology and End Results Program, 18 Registries (SEER-18) database from the National Cancer Institute's SEER Program. Since 1973, the SEER program has collected data on cancer incidence and mortality from various population-based cancer registries across the US. The SEER-18 database includes patients diagnosed with cancer from 2000 – 2018 incorporating data from 18 state and regional registries, representing 27.8% of the US population [7].

The present analysis included persons aged 45 years and older diagnosed with melanoma between 2000 and 2013 and followed up through 2018. Melanoma was identified using ICD-O-3 site codes C440-C449. SEER-18 included data on patients diagnosed from 2000 to 2018, and we restricted our analysis to patients diagnosed with melanoma between 2000 and 2013 to ensure at least 5 years of follow-up data for each patient. We restricted our analysis to individuals 45 years and older since less than 5% of melanomas are diagnosed in persons less than 45 years old. We excluded patients diagnosed on autopsy, death certificate, with unknown diagnostic confirmation, unknown survival time, unknown cause of death, secondary diagnosis of melanoma, and who were alive after the cut-off date of Dec 31, 2018. To classify cause of death, the SEER program used the International Classification of Diseases, tenth edition (ICD-10) diagnosis codes. We included the ten most common non-melanoma causes of death: heart disease, lung and bronchial cancer, cerebrovascular disease, Alzheimer's disease, chronic and obstructive pulmonary disease, diabetes mellitus, accidents and adverse events, pneumonia and influenza, nephritis, nephrotic syndrome, and nephrosis, and pancreatic cancer. The study was approved by the Institutional Review Board of the University of Massachusetts Chan Medical School.

Statistical Analysis

Population characteristics were determined for patients diagnosed with melanoma during the period under study and examined according to cause of death. We analyzed all causes of death, and further categorized cause of death as either melanoma-specific or attributed to another cause. Follow-up time was calculated from the date of melanoma diagnosis to date of death, loss to follow-up, or end of study period (December 31, 2018). The proportion of deaths according to cause of death was calculated with the numerator representing cumulative incidence of death for a specific cause and denominator representing the total number of deaths from all causes.

We calculated age-adjusted mortality rates using the 2000 US Standard Population. The Joinpoint Regression Program from the National Cancer Institute was used to determine the line of best fit through age-adjusted mortality rates by calendar year and through proportion of deaths by years since diagnosis [8]. Annual percent change (APC) in mortality rates and proportion of deaths were calculated using joinpoint regression analysis. The age-adjusted mortality rates of melanoma-specific death and other-cause specific death, overall and by the 10 most frequent non-melanoma causes, were examined by calendar year. We also stratified trends in mortality by sex and the four regions of the US as defined by the U.S. Bureau of the Census (northern, midwestern, western, southern) [9]. Stratification by age was examined using crude mortality rates rather than age-adjusted rates to avoid over-adjustment by age. To determine the prevalence of patients aged 45 years or older diagnosed with melanoma, 5-year limited duration prevalence estimates were extracted from the SEER*Stat program from the National Cancer Institute. Stata 17 was used for all other analyses.

CHAPTER III: RESULTS

A total of 198,360 cases of melanoma cases were diagnosed between 2000 – 2013. Cases diagnosed on autopsy, death certificate, or with unknown diagnostic confirmation (n= 990), cases with unknown survival time after diagnosis (n= 798), cases with unknown cause of death (n= 789), and cases with a secondary diagnosis of melanoma (n= 45,881) were excluded from the analysis. Patients who were alive after the cut-off date of Dec 31, 2018 were not included in the analysis (n= 97,227). Taken together, this resulted in a final analytic sample of 52,675 patients diagnosed with melanoma.

Melanoma was diagnosed more often in males than females (60.3% and 39.7%), and the median age of diagnosis was 74 years old. A greater proportion of melanoma-specific death occurred in males (68.9%) than in females (31.1%) and a greater proportion of other cause-specific death occurred in males (65.5%) than in females (34.5%) (Table 1). For all patients diagnosed with melanoma, the median overall survival time was 4.1 years after diagnosis and the median age of death was 78 years old. A greater proportion of patients with melanoma died from other causes (68.8%) than from melanoma overall in 2005 – 2018 (31.1%). The median age of other-cause specific death (74 years) was higher than that of melanoma-specific death (66 years). The median survival time for patients who died from causes other than melanoma (5.3 years) was longer than that of patients who eventually died from melanoma (2.2 years, $p < 0.001$) (Table 1).

Summary of Mortality Trends

Within the first year after diagnosis, patients with melanoma were more likely to die from melanoma than from other causes of death. With more than 1 year of follow-up, patients were instead more likely to die from other causes than from melanoma. Approximately one year after diagnosis, the proportion of deaths due to other causes was higher than the proportion of deaths

from melanoma, and the proportion of other-cause specific death continued to increase until the end of the study period (Figure 1, Table S1). Among other causes of death, the most common cause of non-melanoma death in these patients was heart disease, followed by lung and bronchial cancer, and then cerebrovascular disease (Figure 2, Table S2).

Both melanoma-specific and other cause-specific age-adjusted mortality rates decreased over the study period. The melanoma-specific mortality rate decreased by an average of 10.1% per year from 2005 – 2014, followed by a steeper decline by an average of 39.1% per year from 2014 – 2018 (Figure 3a, Table S3a). For all other cause-specific mortality rates combined, there was a decrease of 2.8 % from 2005 – 2014, followed by a steeper decline of 34.9% from 2014 – 2018. Among other causes of death, heart disease and lung/bronchial cancer were most frequent. Among the ten most frequent other causes of death, approximately 45% of patients died from heart disease and 10% died from lung disease. For heart disease-specific mortality, there was a decrease of 4.0% from 2005 – 2014 and a decrease of 31.3% from 2014 – 2018. For lung and bronchial cancer-specific mortality, there was a decrease of 5.5% from 2005 – 2014, followed by a decrease of 36.2% from 2014 – 2018. Trends in the ten most common non-melanoma causes of death are detailed in Figure 3b and Table S3b.

Cause-specific mortality trends stratified by sex

While males had a higher mortality rate from melanoma at various timepoints as compared with females, males experienced a greater decline in melanoma-specific mortality during recent years. For males, the melanoma-specific mortality rate decreased by 9.1% per year in 2005 – 2014, followed by a steeper decline of 39.4% per year from 2014-2018. For females, the melanoma-specific mortality rate decreased by 9.2% per year in 2005-2013, followed by steeper drops of 34.6% in 2013-2018. For other cause-specific mortality combined, there was a decrease of 2.5%

per year from 2005 – 2016 and 34.7 % in 2016 -2018 for males. For females, there was a decrease of 2.5% per year from 2005 – 2013 and 34.1% in 2013 – 2018 (Figures 4 and S1, Table S4).

Cause-specific mortality trends stratified by age

In examining the mortality rates according to age, persons aged 45 – 54 years experienced the lowest mortality rate from 2005 – 2018 while those aged 75 years and older had the highest mortality rate during this period. Each age group exhibited a marked decline in melanoma-specific mortality around 2014, with the largest decline from 2014-2018 seen among those aged 75 years and older with an APC of -48.1%. Other-cause mortality remained relatively stable among those younger than 64 years old, but decreased among those aged 65 – 75 years and older than 75 years, by 2.0% in 2005 – 2016 and 31.9% in 2016 – 2018, and 5.3% in 2005 – 2016 and 43.3% in 2016-2018, respectively (Figures 5 and S2, Table S5).

Cause-specific mortality trends stratified by region of the US

In examining trends in mortality by region of the US, patients residing in the southern region of the US had a higher mortality rate at the start of the study period as compared with persons residing in all other regions, for both melanoma-specific and other cause-specific mortality. The melanoma-specific mortality rates were 2,452 in southern regions, per 100,000, as compared to 2,272, 2,185, and 2,312 in northeastern, midwestern, and western regions, per 100,000. The non-melanoma-specific mortality rates were 2,806 in southern regions, per 100,000, as compared to 2,170, 2,382, and 2,288 in northeastern, midwestern, and western regions, per 100,000. For the southern regions, where UV exposure may be greater, melanoma-specific mortality rate decreased by 27.7% from 2013 – 2016, followed by a stepper decline of 46.9% from 2014 – 2018. Other cause-specific mortality decreased by 33.6 % from 2016 – 2018. For all regions

by the end of the study period, melanoma-specific and other-cause mortality had declined markedly starting in 2014, and the 2018 rates were relatively similar (Figures 6 and S3, Table S6).

CHAPTER IV: DISCUSSION

Overall cause-specific mortality trends

We examined trends in cause of death among patients aged 45 and older with primary melanoma from 2005 – 2018. We observed that patients were more likely to die from other causes of death than from melanoma with increasing time since diagnosis. The proportion of deaths from causes other than melanoma was higher than that of melanoma-specific death beginning around 1 year following diagnosis, and this difference continued to increase until the end of the study period. In harmony with this finding, the decrease in mortality from melanoma was much steeper than that from other causes of death, particularly starting in 2014. In sex stratified analyses, males had a higher mortality rate than females consistently, and a steeper decline in melanoma-specific mortality throughout the study period. For other cause mortality, males and females had relatively similar decline in mortality until 2016, when males started to have a slightly steeper decline as compared to females. In analyses stratified by age, each age group exhibited a decline in melanoma-specific mortality over the study period, with the steepest decline observed among those 75 years and older. For other-cause mortality, rates were relatively stable among those younger than 64, but decreased among those aged 65 and older over time. Among region stratification, patients living in southern regions of the US had higher mortality rates overall as compared to those living in other regions.

There was a marked decline in melanoma-specific mortality particularly starting around 2013-2014, which may correspond with the introduction of multiple advanced treatments for melanoma in 2011. Between 1974 to 1999, only 4 drugs were approved by the FDA for melanoma treatment. This is contrast to the 10 FDA-approved therapies, including selective inhibitors, antibodies, and combined therapies, starting in 2011 [10, 11]. In fact, the treatment landscape for

melanoma is continuing to evolve. While the initial use of biologic therapy saw potential for prolonging survival for patients with melanoma due to rapid reduction in tumor size, progress was tempered by later progression of the cancer. In response, dual therapy was implemented, which led to an improvement in rates of progression-free survival [12-15]. Additionally, with increased survival time since diagnosis, we observed an increasingly higher proportion of deaths from non-melanoma cases. This may reflect the influence of treatment advances on improving survival in patients diagnosed with melanoma, especially among those with advanced melanoma, thereby increasing the proportion of deaths from non-melanoma causes.

Regarding the distribution of non-melanoma causes of death, heart disease was the leading cause of death in patients diagnosed with melanoma, as it is in the general US population [16]. In fact, the majority of non-melanoma causes of death had similar mortality distribution as that of the general US population, including causes such as lung, cerebrovascular, kidney and Alzheimer's disease. Among non-melanoma cancer-specific causes of death, lung and pancreatic cancer were leading causes. While the most common causes of cancer mortality in the US population does frequently include lung and pancreatic cancer, there are also more common cancers like breast, prostate, and colon cancer that were not observed as leading causes in our study population. This is potentially due to longer survival time in these cancers which were not captured within our study period, whereas the 5-year survival rate for lung and pancreatic cancers are among the lowest of all cancers [17].

Cause-specific mortality trends stratified by sex

When stratified by sex, a trend similar to the unstratified model was observed. Non-melanoma cause of death remained the leading cause of death throughout the entire study for both males and females. The age-adjusted overall mortality rate was consistently higher in males than

females. This reflects previous findings that have suggested a melanoma-host difference, with the probability of progressing to distant metastasis significantly lower in females as compared to males [18]. We also observed that the mean age of melanoma diagnosis and of death from all causes was higher for females as compared to males.

Of note, previous literature has also shown that the mortality rate of males aged younger than 65 years living in socioeconomically disadvantaged US counties did not decline following the 2011 FDA drug approval at the same rate as compared to females across all ages and socioeconomic status. While this difference possibly reflects a cancer-host disadvantage, it may also reflect a social production of disease process suggesting that females' survivorship advantage may be due to better access to healthcare [17]. Thus, if this melanoma-host difference is limited to lower SES counties, which should be confirmed in other studies, the observed difference in mortality may be more likely due to socioeconomic factors such as access to healthcare and health insurance.

Cause-specific mortality trends stratified by age

Among those aged 45 – 54, melanoma was the leading cause of death among patients with melanoma until around 2015, at which point the leading cause of death was overtaken by heart, lung, cerebrovascular disease and various cancers. A similar trend was observed among patients aged 55 – 64, when non-melanoma causes exceeded melanoma as cause of death beginning around 2014. Conversely, among those aged 65 and older, non-melanoma causes were the leading causes of death from 2005-2018. A similar pattern was observed for those patients aged 75+, with non-melanoma causes contributing to more deaths throughout the entire study period. With increasing age, non-melanoma causes were more likely to be the leading cause of death. The overall mortality rate was also greater with increasing age, which is consistent with national mortality trends [19].

Notably, the melanoma-specific mortality rate was higher as compared to the other-cause mortality rate among younger patients from 2005 – 2015 in those aged 45 – 54 years and from 2005 – 2014 in those aged 55 – 64 years. This may reflect a trend consistent with previous literature showing that younger patients are more likely to have melanoma with severe high-risk primary features, such as ulceration or increased thickness [20]. These characteristics could explain the greater proportion of deaths from melanoma in younger patients that was observed. As seen in previous literature, older patients are still expected to have an overall higher melanoma mortality rate, given decreased host immune function and greater multimorbidity burden, among other age-related effects on survivorship [21].

Cause-specific mortality trends stratified by region of the US

Among region stratification as designated by the Census Bureau Regions and Divisions with State FIPS Codes, each region reflected similar findings to the unstratified model. Trends in melanoma mortality were relatively similar across all regions, with a marked decline around 2014. Among non-melanoma cause of death, heart disease was the leading cause across all strata throughout the entire study period. The southern regions had the highest rates of non-melanoma death as compared to northern, mid-western, and western regions before 2014, which corroborates patterns of overall mortality in southern regions spanning 1965-2014 [22]. After 2014, however, the melanoma and non-melanoma mortality rates were relatively similar across all regions, suggesting that regional disparities may be lessening. Of note, the gradient difference in melanoma incidence by ambient UV exposure has also been thought to be decreasing over time. In fact, coastal regions have been shown to have even higher incidence of melanoma than southern regions, despite lower ambient UV exposure [23]. Given that our regional strata do not allow for

the separate assessment of coastal states, we were unable to test this hypothesis, even if there was

an initial UV-dependent difference in melanoma disease severity.

CHAPTER V: CONCLUSIONS

Study strengths and limitations

Due to comprehensive population-level cancer data and patient demographics available from SEER, we were able to analyze cases with known diagnostic confirmation, reporting source, known survival months, and primary cancer confirmation. Moreover, the study period of 2000 – 2018 allowed for at least 5 years of follow-up time for each case to capture mortality years after diagnosis, given the high 5-year survival rate among patients with melanoma.

Study limitations included the restricted number of cases available for analysis, especially when stratifying by age and region, and precluded an analysis by race/ethnicity. Moreover, melanoma prevalence estimates were based on limited-duration prevalence, which shows the proportion of people with melanoma over a specified time period. This may decrease mortality estimates, although relative proportions would not be affected. We limited our analysis to cases of primary melanoma with known diagnostic confirmation, reporting source, and known survival months; however, misclassifications in these categories, although likely rare, could under- or overestimate mortality. We also lacked access to detailed individual-level treatment data, which would help illustrate the hypothesized influence of new melanoma treatment options on declining melanoma-specific mortality rates.

Future directions

Our data shows that patients aged 45 and older with melanoma are more likely to die from non-melanoma causes of death, such as heart, lung, and kidney disease, than from melanoma itself. This trend is seen even among various strata of age, sex and geographic region. Mortality rates among patients with melanoma decreased overall within this study period. Although the introduction of new therapies during the study period likely made a difference in the survival of

those diagnosed with melanoma, it remains to be seen if all groups of people are able to benefit from this treatment. Moreover, we also observed an overall decrease in both melanoma and non-melanoma mortality throughout the study period, potentially due to a decrease in mortality within the SEER population as a whole, alongside improvements in detection of early-stage melanoma that resulted in better treatment outcomes and longer survival. In fact, the increasing use of technologies such as computer-assisted dermoscopy may have also served to enhance accuracy in diagnosis of melanoma and potentially reduce delays in treatment. These digital methods utilize artificial intelligence systems, which allows for detailed analysis of lesions and even computation of risk-scores [24, 25]. These advances in diagnosis may contribute to the earlier detection of melanoma and preclude progression to later stages that are more difficult to treat. Future multi-center studies may serve to further clarify the relationship between screening improvements, behavioral changes, genetic risk factors, and race/ethnicity with survival time, response and access to treatment, and causes of melanoma mortality.

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TABLES AND FIGURES

Population Characteristics	Died from All Causes		Died from Melanoma		Died from Other Causes	
	N	**%**	**N**	**%**	**N**	**%**
All patients	52675	100	17289	31.1%	35386	68.8%
Male	35096	66.6	11912	68.9	23184	65.5
Female	17579	33.4	5377	31.1	12202	34.5
Median age at diagnosis, years	74		66		76	
Age at diagnosis, years						
45-49	2391	4.5	1530	8.8	861	2.4
50-54	3227	6.1	1960	11.3	1267	3.6
55-59	4038	7.7	2088	12.1	1950	5.5
60-64	4949	9.4	2224	12.9	2725	7.7
65-69	5916	11.2	2188	12.7	3728	10.5
70-74	7135	13.6	2051	11.9	5084	14.4
75-79	8423	16.0	2043	11.8	6380	18.0
80-84	8267	15.7	1726	10.0	6541	18.5
85+	8329	15.8	1479	8.6	6850	19.4
Year of diagnosis						
2000-2004	21157	40.2	6215	36.0	14942	38.9
2005-2009	19389	36.8	6434	37.2	12955	39.0
2010-2013	12129	23.0	4640	26.8	7489	22.1
Median age at death, years	78		68		81	
Median survival time, years	4.1		2.2		5.3	

Table 1
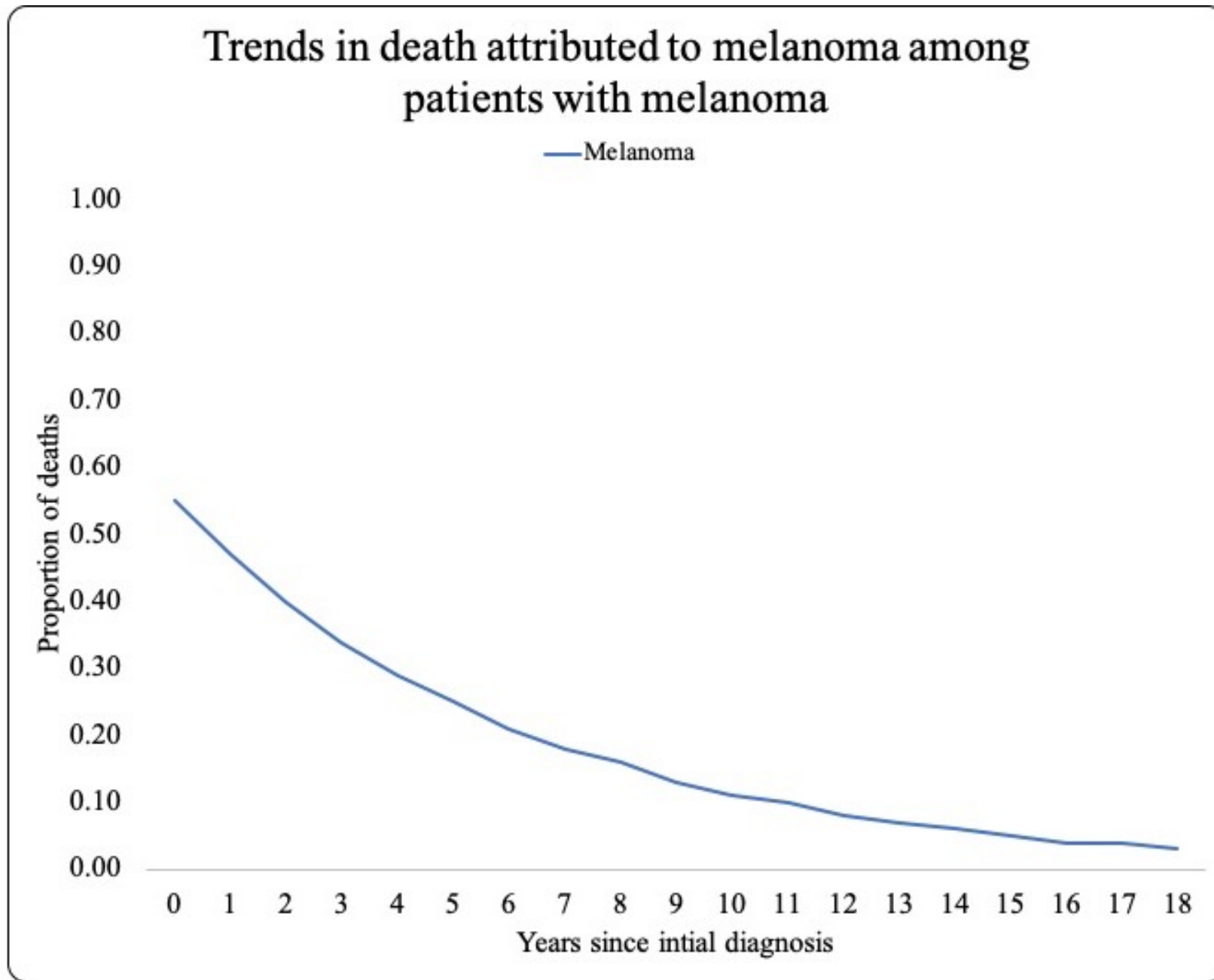
Figure 1. Proportion of deaths attributed to melanoma among US SEER patients diagnosed with melanoma from 2000 – 2013, by years since the initial diagnosis.
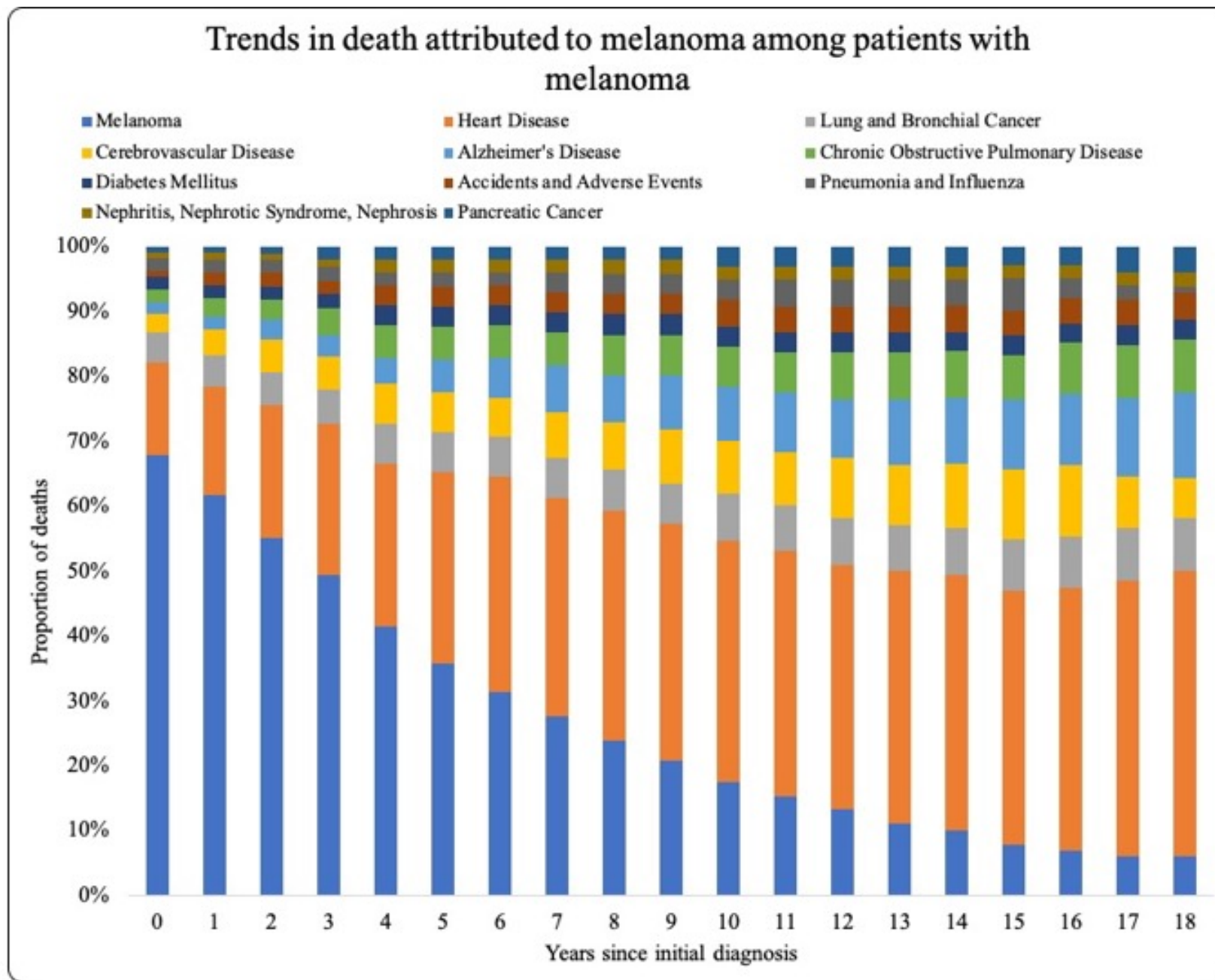
Figure 2. Proportion of deaths attributed to melanoma and non-melanoma causes. Estimates are among the 11 most frequent causes of death of US SEER patients diagnosed with melanoma from 2000 – 2013.

Figure 3.

a) Age-adjusted annual rates* of death from melanoma and other causes in the United States SEER population, by year of death 2005 – 2018, using Joinpoint regression.

b) Age-adjusted annual rates* of death from melanoma and ten most common other causes in the United States SEER population, by year of death 2005 – 2018, using Joinpoint regression.

*per 100,000 diagnosed with melanoma

Figure 4.
Age-adjusted annual rates* of death from melanoma and ten most common other causes in the United States SEER population, by year of death 2005 – 2018, using Joinpoint regression.
*per 100,000 diagnosed with melanoma

Figure 5.
Age-adjusted annual rates* of death from melanoma and ten most common other causes among various age groups in the United States SEER population, by year of death 2005 – 2018, using Joinpoint regression.
*per 100,000 diagnosed with melanoma
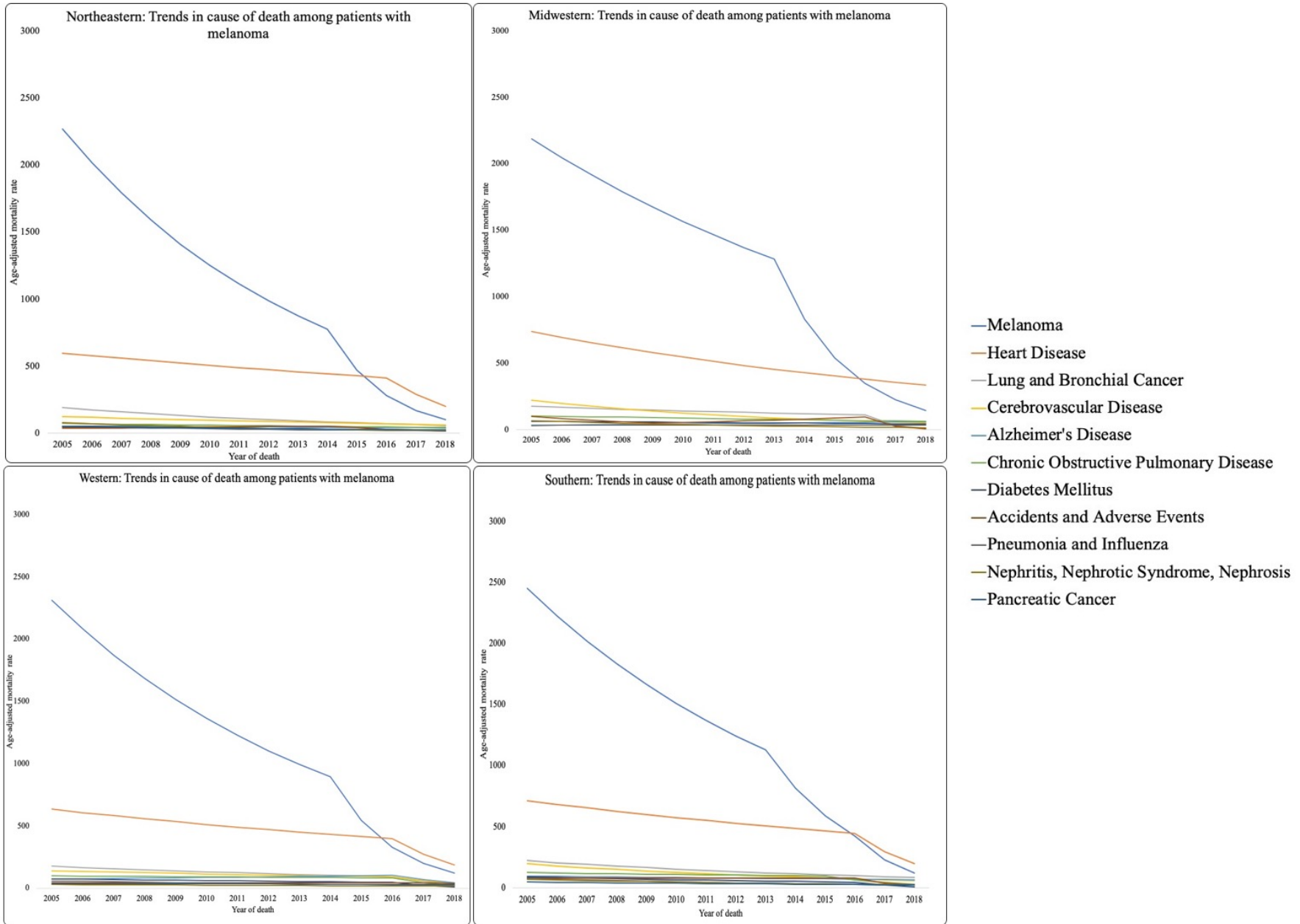
Figure 6.
Age-adjusted annual rates* of death from melanoma and ten most common other causes among various regions in the United States SEER population, by year of death 2005 – 2018, using Joinpoint regression.
*per 100,000 diagnosed with melanoma

SUPPLEMENTAL FIGURES AND TABLES
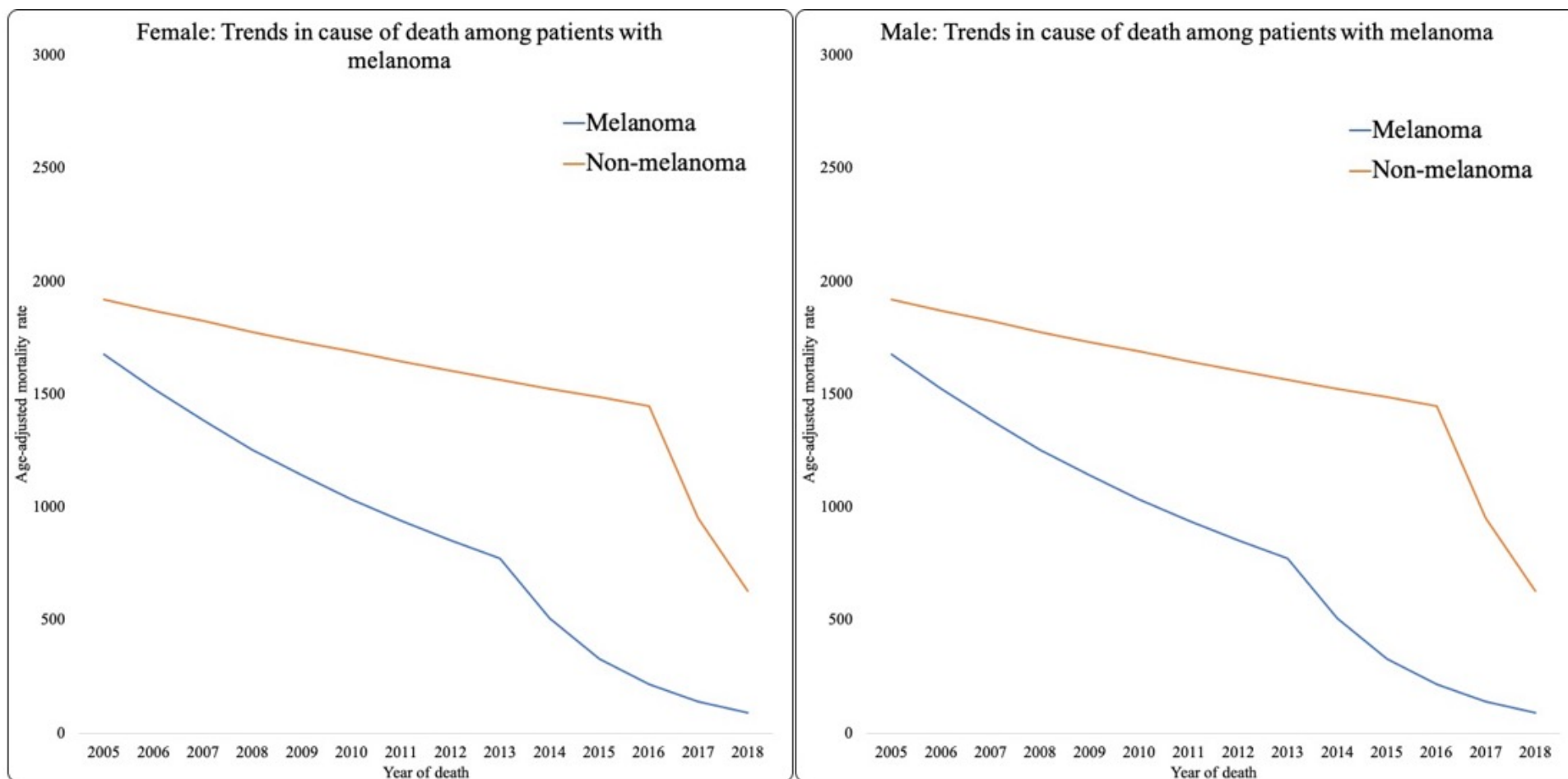
Supplemental Figure 1.

Age-adjusted annual rates* of death from melanoma and other causes among males and females in the United States SEER population, by year of death 2005 – 2018, using Joinpoint regression.
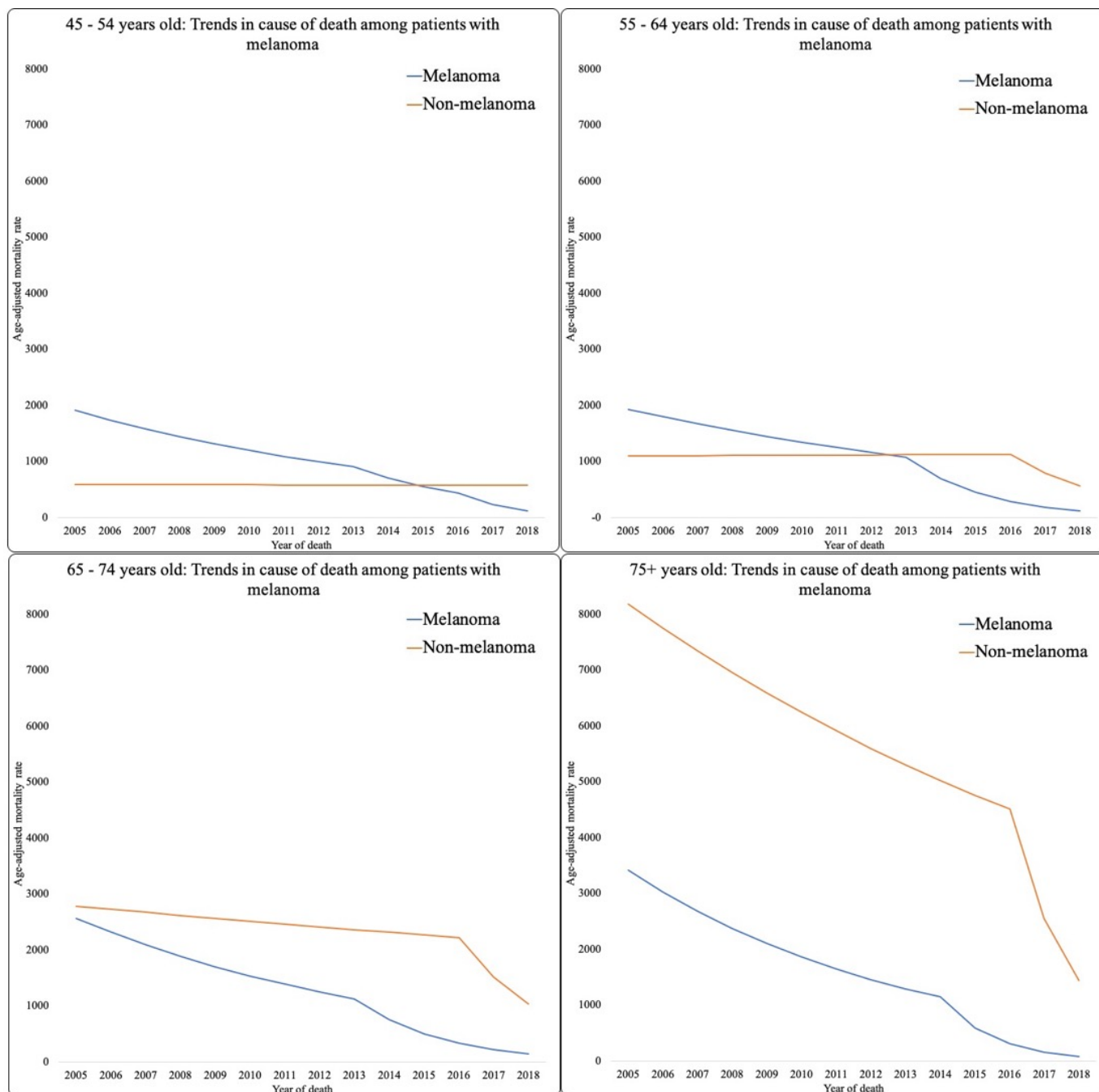
Supplemental Figure 2.
Crude annual rates* of death from melanoma and other causes among various age groups in the United States SEER population, by year of death 2005 – 2018, using Joinpoint regression.
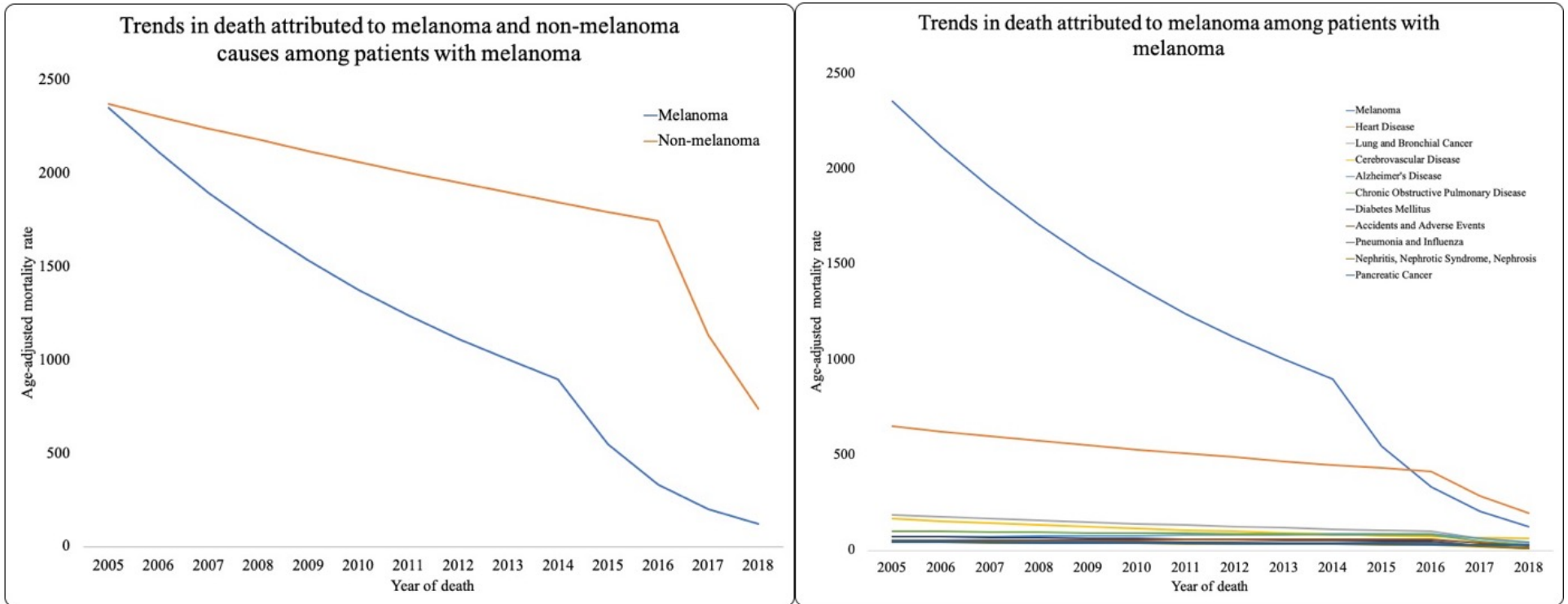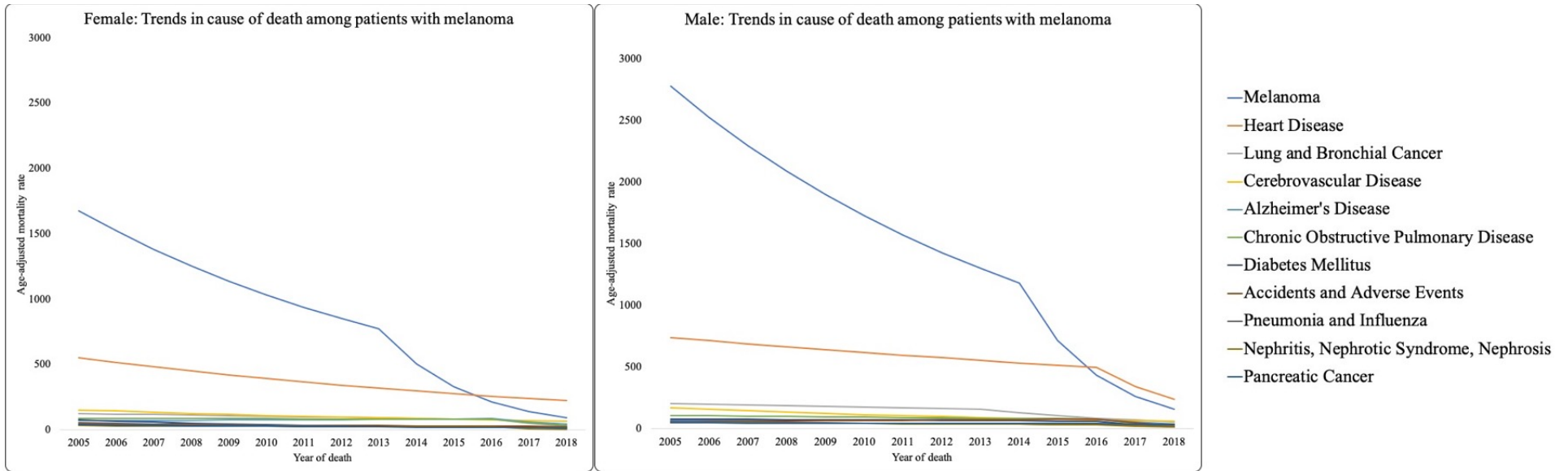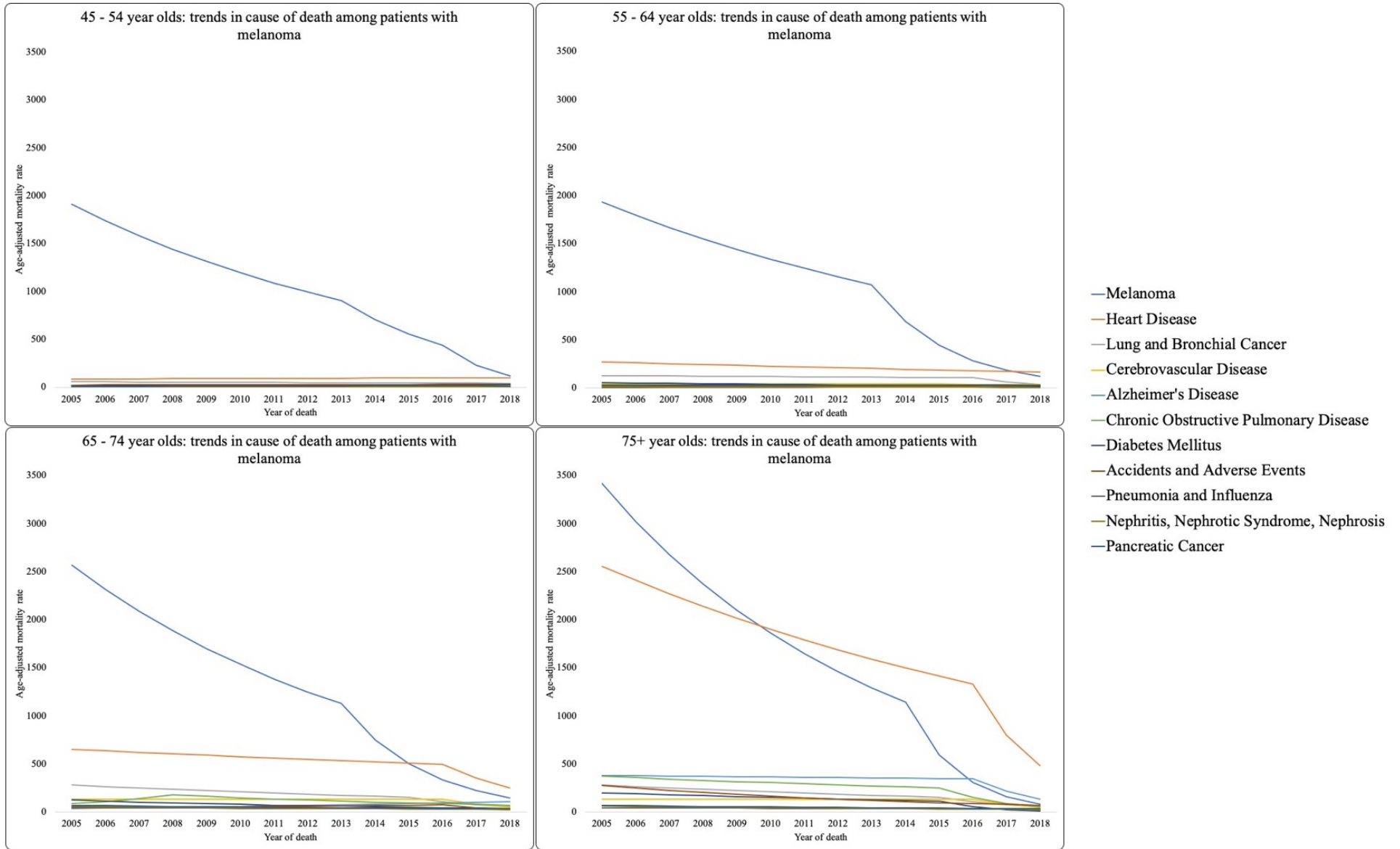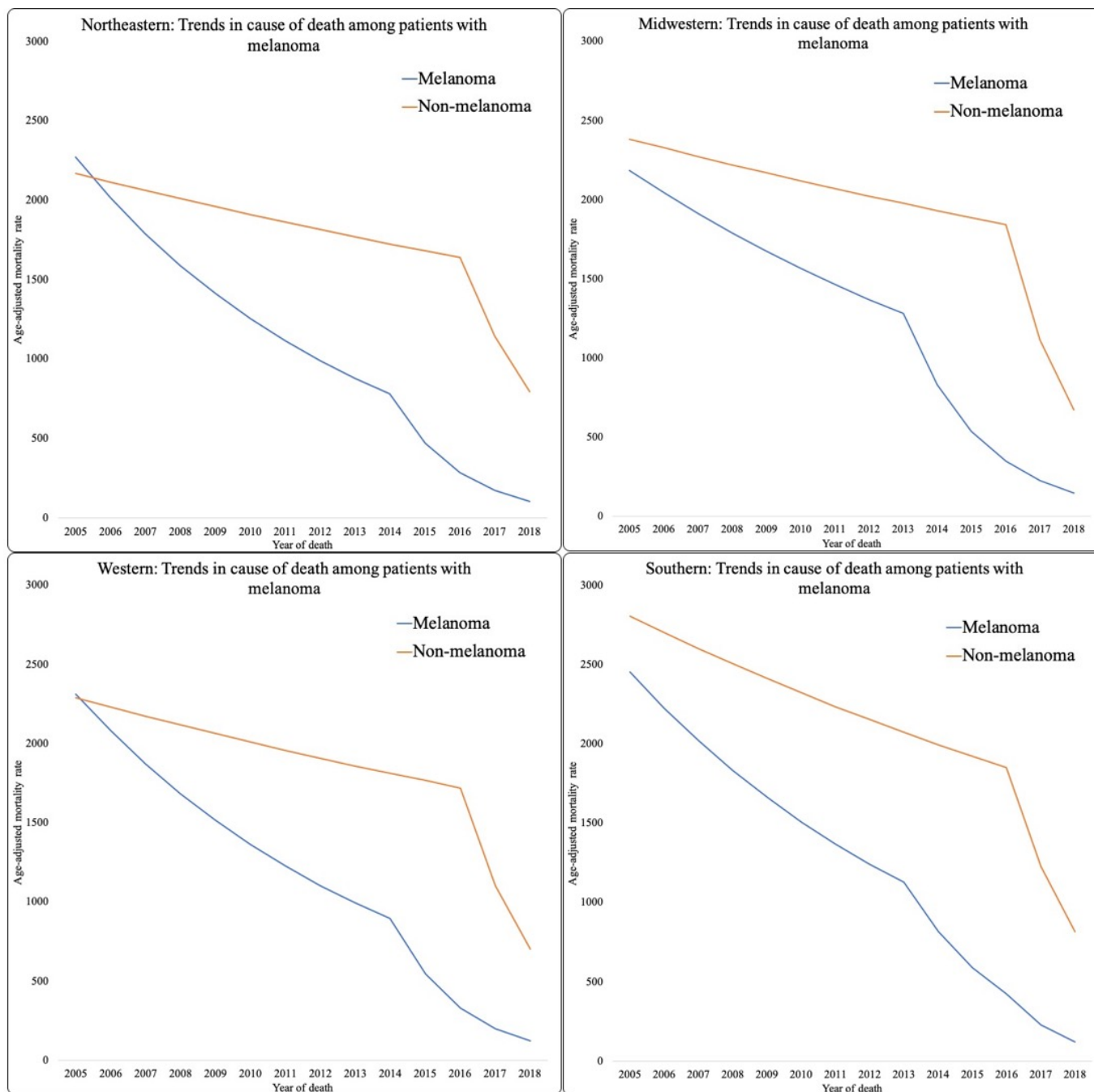
Supplemental Figure 3.
Age-adjusted annual rates* of death from melanoma and other causes among various regions in the United States SEER population, by year of death 2005 – 2018, using Joinpoint regression.

Table S1.		
	Segment	Annual Percent Change (95% CI)
Death from melanoma	0-18	-14.6 (-16.1, -13.1)
Death from other causes	0-4	13.1 (11.6, 14.6)
	4-8	4.6 (2.5, 6.8)
	8-16	1.5 (1.0, 2.1)
	16-18	-1.3 (-5.2, 2.9)

Table S2.		
	Segment	Annual Percent Change (95% CI)
Death from melanoma	0-18	-13.3 (-14.8, -11.8)
Death from heart disease	0-6	13.5 (10.7, 16.3)
	6-18	2.2 (1.4, 3.1)
Death from lung cancer	0-18	2.8 (0.5, 5)
Death from cerebrovascular disease	0-2	29.9 (2.8, 64)
	2-16	5.6 (4.4, 6.9)
	16-18	-24.8 (-40.4, -5)
Death from Alzheimer's disease	0-6	26.2 (17.3, 35.8)
	6-18	5.9 (3.2, 8.6)
Death from chronic obstructive pulmonary disease	0-4	20.5 (4, 39.5)
	4-18	3.6 (1.3, 5.8)
Death from diabetes mellitus	0-18	2.2 (-0.7, 5.1)
Death from accidents and adverse events	0-5	20.6 (7.0, 35.9)
	5-18	2.2 (-0.7, 5.1)
Death from pneumonia and influenza	0-15	8.0 (4.7, 11.5)
	15-18	-36.2 (-56.0, -7.5)
Death from nephritis, nephrotic syndrome, and nephrosis	0-6	16.3 (4.1, 29.9)
	6-18	-0.1 (-3.9, 3.9)
Death from pancreatic cancer	0-3	46.5 (-1.4, 117.8)
	3-18	4.9 (1.4, 8.5)

Table S3a.		
	Calendar period	Annual Percent Change (95% CI)
Death from melanoma	2005-2014	-10.1 (-13.7, -6.4)
	2014-2018	-39.1 (-47.1, -29.8)
Death from other causes	2005-2016	-2.8 (-3.6, -1.9)
	2016-2018	-34.9 (-42.5, -26.2)
Table S3b.		
	Calendar period	Annual Percent Change (95% CI)
Death from melanoma	2005-2014	-10.1 (-13.7, -6.4)
	2014-2018	-39.1 (-47.1, -29.8)
Death from heart disease	2005-2016	-4.0 (-5.1, -3.0)
	2016-2018	-31.3 (-41.7, -19.1)
Death from lung cancer	2005-2016	-5.5 (-7.2, -3.8)
	2016-2018	-36.2 (-51.3, -16.4)
Death from cerebrovascular disease	2005-2018	-7.2 (-9.9, -4.3)
Death from Alzheimer's disease	2005-2016	2.0 (0.0, 4.0)
	2016-2018	-28.7 (-47.0, -4.1)
Death from chronic obstructive pulmonary disease	2005-2016	-2.2 (-4.7, 0.4)
	2016-2018	-40.8 (-59.6, -13.3)
Death from diabetes mellitus	2005-2016	-3.8 (-7.4, -0.1)
	2016-2018	-51.6 (-72.4, -15)
Death from accidents and adverse events	2005-2016	1.1 (-2.6, 5.0)
	2016-2018	-37.8 (-64.4, 8.6)
Death from pneumonia and influenza	2005-2016	-3.1 (-6.7, 0.6)
	2016-2018	-40.8 (-66.1, 3.6)
Death from nephritis, nephrotic syndrome, and nephrosis	2005-2016	-3.4 (-5.7, -1.1)
	2016-2018	-42.6 (-59.5, -18.7)
Death from pancreatic cancer	2005-2018	-3.2 (-5.5, -0.8)

Table S4.		
Female		
	Calendar period	Annual Percent Change (95% CI)

Death from melanoma	2005-2013	-9.2 (-11.9, -6.4)
	2013-2018	-34.6 (-38.5, -30.4)
Death from other causes	2005-2016	-2.5 (-3.0, -2.0)
	2016-2018	-34.1 (-39.1, -28.6)
Death from heart disease	2005-2018	-6.7 (-9.4, -3.9)
Death from lung cancer	2005-2016	-3.9 (-7.9, 0.3)
	2016-2018	-36.3 (-66.3, 20.2)
Death from cerebrovascular disease	2005-2018	-6.2 (-9.0, -3.3)
Death from Alzheimer's disease	2005-2018	0.1 (-3.8, 4.2)
Death from chronic obstructive pulmonary disease	2005-2016	-0.9 (-3.5, 1.6)
	2016-2018	-33.1 (-54.3, -1.9)
Death from diabetes mellitus	2005-2018	-11.3 (-17.1, -5.1)
Death from accidents and adverse events	2005-2018	-4 (-8.3, 0.5)
Death from pneumonia and influenza	2005-2018	-8.7 (-14.0, -3.0)
Death from nephritis, nephrotic syndrome, and nephrosis	2005-2016	-3.1 (-6.6, 0.5)
	2016-2018	-49.1 (-70.4, -12.6)
Death from pancreatic cancer	2005-2018	-6.1 (-9.8, -2.2)
Males		
	Calendar period	Annual Percent Change (95% CI)
Death from melanoma	2005-2014	-9.1 (-13.6, -4.3)
	2014-2018	-39.4 (-49.2, -27.7)
Death from other causes	2005-2016	-2.5 (-3.5, -1.5)
	2016-2018	-34.7 (-44.3, -23.5)
Death from heart disease	2005-2016	-3.6 (-4.8, -2.3)
	2016-2018	-30.6 (-42.5, -16.3)
Death from lung cancer	2005-2013	-3.0 (-6.2, 0.3)
	2013-2018	-18.7 (-24.1, -12.8)
Death from cerebrovascular disease	2005-2018	-7.6 (-10.7, -4.5)
Death from Alzheimer's disease	2005-2016	1.8 (0.1, 3.4)
	2016-2018	-29.4 (-44.6, -10.0)
Death from chronic obstructive pulmonary disease	2005-2016	-2.8 (-5.7, 0.3)
	2016-2018	-46.6 (-66.3, -15.5)
Death from diabetes mellitus	2005-2016	-2.4 (-6.5, 1.8)
	2016-2018	-51.8 (-74.4, -9.3)

Death from accidents and adverse events	2005-2016	3.0 (-2.7, 9.0)
	2016-2018	-40.5 (-74.2, 37.5)
Death from pneumonia and influenza	2005-2018	-5.8 (-10.1, -1.3)
Death from nephritis, nephrotic syndrome, and nephrosis	2005-2016	-4.0 (-7.7, -0.1)
	2016-2018	-39.6 (-66.5, 8.7)
Death from pancreatic cancer	2005-2018	-1.3 (-4.8, 2.3)

Table S5.		
45 – 54 years old		
	Calendar period	Annual Percent Change (95% CI)
Death from melanoma	2005-2013	-8.9 (-10.5, -7.3)
	2013-2016	-21.5 (-33.3, -7.7)
	2016-2018	-48.0 (-55.8, -38.8)
Death from other causes	2005-2018	-0.2 (-3.4, 3.2)
Death from heart disease	2005-2018	1.3 (-2.0, 4.7)
Death from lung cancer	2005-2018	-2.5 (-7.2, 2.4)
Death from cerebrovascular disease	2005-2018	-7.1 (-17.6, 4.6)
Death from Alzheimer's disease	2005-2018	9.9 (0.7, 19.9)
Death from chronic obstructive pulmonary disease	2005-2018	6.2 (-3.4, 16.7)
Death from diabetes mellitus	2005-2018	-1.7 (-12.1, 10.1)
Death from accidents and adverse events	2005-2018	2.5 (-5.2, 10.8)
Death from pneumonia and influenza	2005-2018	-4.1 (-10.7, 3)
Death from nephritis, nephrotic syndrome, and nephrosis	2005-2018	-4.1 (-13.1, 5.8)
Death from pancreatic cancer	2005-2018	8.6 (-0.4, 18.5)
55 – 64 years old		
	Calendar period	Annual Percent Change (95% CI)
Death from melanoma	2005-2013	-7.0 (-11.8, -2)
	2013-2018	-35.6 (-42.2, -28.3)
Death from other causes	2005-2016	0.3 (-1.0, 1.6)
	2016-2018	-29.5, (-41.9, -14.6)
Death from heart disease	2005-2018	-3.6 (-6.4, -0.8)
Death from lung cancer	2005-2016	-1.9 (-5.8, 2.1)
	2016-2018	-39.6 (-66.9, 10.1)

Death from cerebrovascular disease	2005-2018	-0.6 (-5.2, 4.1)
Death from Alzheimer's disease	2005-2018	10.9 (2.1, 20.5)
Death from chronic obstructive pulmonary disease	2005-2018	0.2 (-6.5, 7.4)
Death from diabetes mellitus	2005-2018	-7.1 (-12.4, -1.5)
Death from accidents and adverse events	2005-2018	1.2 (-4.7, 7.4)
Death from pneumonia and influenza	2005-2016	13.5 (3.7, 24.3)
	2016-2018	-60.1 (-89.7, 53.8)
Death from nephritis, nephrotic syndrome, and nephrosis	2005-2018	-5.4 (-12.9, 2.7)
Death from pancreatic cancer	2005-2018	-0.5 (-3.8, 2.9)
65 - 74 years old		
	Calendar period	Annual Percent Change (95% CI)
Death from melanoma	2005-2013	-9.8 (-13.1, -6.3)
	2013-2018	-33.4 (-38.3, -28.1)
Death from other causes	2005 - 2016	-2.0 (-3.0, -1.0)
	2016 - 2018	-31.9 (-41.4, -20.8)
Death from heart disease	2005-2016	-2.5 (-3.9, -1.0)
	2016-2018	-28.7 (-42.8, -11.2)
Death from lung cancer	2005-2015	-5.7 (-9.6, -1.7)
	2015-2018	-29.4 (-46.0, -7.7)
Death from cerebrovascular disease	2005-2016	-0.1 (-3.0, 3.0)
	2016-2018	-37.5 (-60, -2.5)
Death from Alzheimer's disease	2005-2018	8.2 (3.9, 12.7)
Death from chronic obstructive pulmonary disease	2005-2008	27.3 (-10, 79.9)
	2008-2018	-8.6 (-13.4, -3.5)
Death from diabetes mellitus	2005-2018	-8.5 (-13.3, -3.6)
Death from accidents and adverse events	2005-2016	4.1 (-0.1, 8.6)
	2016-2018	-40.8 (-68.1, 9.9)
Death from pneumonia and influenza	2005-2018	-2.7 (-7.3, 2.2)
Death from nephritis, nephrotic syndrome, and nephrosis	2005-2018	-5.9 (-9.6, -2.0)
Death from pancreatic cancer	2005-2018	-5.2 (-8.8, -1.5)
75+ years old		
	Calendar period	Annual Percent Change (95% CI)
Death from melanoma	2005-2014	-11.4 (-16.9, -5.6)

	2014-2018	-48.1 (-58.3, -35.4)
Death from other causes	2005 - 2016	-5.3 (-6.6, -3.9)
	2016 - 2018	-43.4 (-53.9, -30.4)
Death from heart disease	2005-2016	-5.8 (-7.2, -4.3)
	2016-2018	-39.8 (-51.9, -24.7)
Death from lung cancer	2005-2016	-8.1 (-11.5, -4.7)
	2016-2018	-59.3 (-76.5, -29.6)
Death from cerebrovascular disease	2005-2016	-7.6 (-9.4, -5.8)
	2016-2018	-33.7 (-50.1, -11.8)
Death from Alzheimer's disease	2005-2016	-0.9 (-2.9, 1.3)
	2016-2018	-37.1 (-54.0, -14.0)
Death from chronic obstructive pulmonary disease	2005-2015	-3.8 (-8.1, 0.7)
	2015-2018	-39.7 (-55.1, -18.9)
Death from diabetes mellitus	2005-2015	-5.4, (-12.5, 2.3)
	2015-2018	-52.0 (-70.9, -20.7)
Death from accidents and adverse events	2005-2015	-1.6 (-5.6, 2.7)
	2015-2018	-37.7 (-52.5, -18.4)
Death from pneumonia and influenza	2005-2018	-9.8 (-13.9, -5.4)
Death from nephritis, nephrotic syndrome, and nephrosis	2005-2015	-2.0 (-8.4, 4.9)
	2015-2018	-38.2 (-60.0, -4.5)
Death from pancreatic cancer	2005-2015	-5.2 (-10.2, 0.1)
	2015-2018	-30.4 (-50.8, -1.7)

Table S6.		
Northeast		
	Calendar period	Annual Percent Change (95% CI)
Death from melanoma	2005-2014	-11.2 (-15.3, -6.9)
	2014-2018	-39.5 (-48.6, -28.8)
Death from other causes	2005-2016	-3.3 (-5.0, -1.6)
	2016-2018	-30.1 (-46.1, -9.5)
Death from heart disease	2005-2016	-3.3 (-5.0, -1.6)
	2016-2018	-30.1 (-46.1, -9.5)
Death from lung cancer	2005-2018	-8.5 (-12.0, -4.9)
Death from cerebrovascular disease	2005-2018	-5.1 (-8.9, -1.1)

	Calendar period	Annual Percent Change (95% CI)
Death from Alzheimer's disease	2005-2018	-2.2 (-7.4, 3.3)
Death from chronic obstructive pulmonary disease	2005-2018	-3.9 (-8.9, 1.5)
Death from diabetes mellitus	2005-2018	-6.9 (-13.9, 0.6)
Death from accidents and adverse events	2005-2014	4.1 (-6.5, 15.9)
	2014-2018	-23.8 (-47.4, 10.5)
Death from pneumonia and influenza	2005-2018	-7.0 (-12.8, -0.9)
Death from nephritis, nephrotic syndrome, and nephrosis	2005-2018	-10.1 (-14.5, -5.5)
Death from pancreatic cancer	2005-2018	-5.3 (10, -0.4)
Midwest		
	Calendar period	Annual Percent Change (95% CI)
Death from melanoma	2005-2013	-6.4 (-9.2, -3.6)
	2013-2018	-35.2 (-39.1, -31.1)
Death from other causes	2005-2018	-5.9 (-8.8, -2.8)
Death from heart disease	2005-2018	-5.9 (-8.8, -2.8)
Death from lung cancer	2005-2016	-4.1 (-12.4, 4.9)
	2016-2018	-70.7 (-92.4, 12.1)
Death from cerebrovascular disease	2005-2018	-10.8 (-14.9, -6.5)
Death from Alzheimer's disease	2005-2018	4.2 (-4.3, 13.6)
Death from chronic obstructive pulmonary disease	2005-2018	-3.8 (-8.9, 1.6)
Death from diabetes mellitus	2005-2018	-3.1 (-11.4, 6.0)
Death from accidents and adverse events	2005-2009	-16.1 (-30.4, 1.1)
	2009-2016	10 (-0.4, 21.5)
	2016-2018	-74.4 (-85.8, -54.0)
Death from pneumonia and influenza	2005-2018	0.2 (-6.1, 6.9)
Death from nephritis, nephrotic syndrome, and nephrosis	2005-2018	-10.9 (-17.9, -3.3)
South		
	Calendar period	Annual Percent Change (95% CI)
Death from melanoma	2005-2013	-9.3 (-11.0, -7.4)
	2013-2016	-27.7 (-39.7, -13.3)
	2016-2018	-46.9 (-55.7, -36.3)
Death from other causes	2005-2016	-4.2 (-6.4, -2.0)
	2016-2018	-33.5 (-52.6, -6.8)
Death from heart disease	2005-2016	-4.2 (-6.4, -2.0)

	2016-2018	-33.5 (-52.6, -6.8)
Death from lung cancer	2005-2018	-7.1 (10.2, -3.9)
Death from cerebrovascular disease	2005-2018	-8.6 (-11.9, -5.1)
Death from Alzheimer's disease	2005-2018	-2.7 (-6.4, 1.0)
Death from chronic obstructive pulmonary disease	2005-2015	-2.5 (-6.9, 2.1)
	2015-2018	-33.1 (-50.2, -10.2)
Death from diabetes mellitus	2005-2016	-6.2 (-10.0, -2.3)
	2016-2018	-53.4 (-74.7, -14.3)
Death from accidents and adverse events	2005-2016	-0.4 (-3.8, 3.3)
	2016-2018	-47.8 (-69.2, -11.5)
Death from pneumonia and influenza	2005-2018	-9.1 (-14, -4)
Death from nephritis, nephrotic syndrome, and nephrosis	2005-2018	-7.7 (-13.8, -1.2)
Death from pancreatic cancer	2005-2018	-5.0 (-12.5, 3.2)
West		
	Calendar period	Annual Percent Change (95% CI)
Death from melanoma	2005-2014	-10.0 (-14.7, -5.1)
	2014-2018	-39.2 (-49.4, -27.0)
Death from other causes	2005-2016	-4.2 (-5.4, -3.0)
	2016-2018	-31.6 (-43.0, -17.9)
Death from heart disease	2005-2016	-4.2 (-5.4, -3.0)
	2016-2018	-31.6 (-43.0, -17.9)
Death from lung cancer	2005-2016	-5.8 (-8.5, -3.0)
	2016-2018	-37.6 (-59.6, -3.8)
Death from cerebrovascular disease	2005-2016	-4.0 (-6.2, -1.7)
	2016-2018	-32.1 (-52.1, -3.7)
Death from Alzheimer's disease	2005-2016	3.2 (0.4, 6.1)
	2016-2018	-33.6 (-55.8, -0.4)
Death from chronic obstructive pulmonary disease	2005-2016	-1.6 (-5.1, 2.0)
	2016-2018	-45.8 (-68.1, -7.9)
Death from diabetes mellitus	2005-2016	-4.1 (-9.1, 1.2)
	2016-2018	-51.5 (-78.1, 7.8)
Death from accidents and adverse events	2005-2018	-0.2 (-4.9, 4.6)
Death from pneumonia and influenza	2005-2018	-6.9 (-11.5, -2.1)
Death from nephritis, nephrotic syndrome, and nephrosis	2005-2018	-4.2 (-9.2, 1.1)

Death from pancreatic cancer	2005-2018	-0.9 (-5.7, 4.3)

Supplementary Table 7. Race distribution of patients diagnosed with melanoma from the SEER Database 2000 – 2013.						
Population Characteristics	**Died from All Causes**		**Died from Melanoma**		**Died from Other Causes**	
	N	**%**	**N**	**%**	**N**	**%**
All patients	52675	100	17289	31.1%	35386	68.8%
Race						
White	51608	98.0	16787	97.1	34821	98.4
Black	417	1.8	217	1.3	200	0.6
Asian or Pacific Islander	397	1.0	217	1.3	180	0.5
American Indian/Alaskan Native	108	0.2	49	0.3	59	0.2
Unknown	145	0.3	19	0.1	126	1.6