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Original Article

Age-period-cohort Analysis of Cutaneous Malignant Melanoma Incidence in the United States from 1987 to 2016

Ruofei Du[1], Jiayu Guo[1], Jing Li[1] and Jun Lyu[2,3*]

[1]School of Public Health, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, China; [2]Department of Clinical Research, the First Affiliated Hospital of Jinan University, Guangzhou, Guangdong, China; [3]Guangdong Provincial Key Laboratory of Traditional Chinese Medicine Informatization, Guangzhou, Guangdong, China

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Abstract

Background and objectives: The prevalence and fatality rates of cutaneous malignant melanoma (CMM) have been rising, particularly among the elderly. This study analyzes CMM incidence trends in the United States elderly population from 1987 to 2016 to inform prevention and management strategies.

Methods: Using incidence data from the Surveillance, Epidemiology, and End Results database spanning 1989 to 2008, we calculated the age-adjusted standardized population incidence rates for CMM in elderly individuals. The Joinpoint software was employed to estimate annual percent change and analyze trends in CMM incidence among elderly individuals from 1987 to 2016.

Results: The study included 56,997 elderly CMM patients from eight Surveillance, Epidemiology, and End Results registries, of whom 36,726 were male (64.4%). The age-adjusted CMM incidence rate from 2012 to 2016 was 0.99 per 1,000, a 2.8-fold increase from 1987–1991 (95% confidence interval: 2.7–2.9). Incidence rates increased with age and birth cohort, peaking at 1.53 per 1,000 males and 0.59 per 1,000 females aged 85+ during 2012–2016. Birth cohort effects also showed a continuous increase.

Conclusions: This study reveals a substantial increase in CMM incidence rates among the elderly from 1987 to 2016, particularly between 2012 and 2016. Incidence rates escalated with age and birth cohort, with the highest rates observed in individuals aged 85 and older.

Introduction

Skin cancer is the most prevalent malignancy in the United States, with malignant melanoma being a highly aggressive form that originates in melanocytes, the cells responsible for producing skin pigment. Despite advances in treatment that have improved survival rates, malignant melanoma remains the deadliest type of skin cancer, and its global incidence continues to rise. Malignant melanoma can develop in various locations, including the skin, mucous membranes, eyes, and even the meninges. The most common types are cutaneous melanoma, ocular melanoma, and mucosal melanoma.[1,2]

Cutaneous melanomas are further categorized into subtypes, including chronic malignant melanoma, superficial spreading melanoma, nodular melanoma, and acral lentiginous melanoma, each with distinct clinical and histological features.[1] While early diagnosis and appropriate treatment result in a five-year survival rate of 95% for most skin cancers, the incidence and mortality rates of cutaneous malignant melanoma (CMM) are notably higher, accounting for 65% of all skin cancer-related deaths.[3] Though patients with metastatic melanoma face a disheartening 5% long-term survival rate, early detection of CMM offers a much more favorable prognosis, often leading to a complete cure.[3]

The global incidence of malignant melanoma has been increasing, with significant demographic disparities. In Western countries such as New Zealand and Australia, the incidence rates are among the highest, with age-standardized rates of 40.2/100,000 and 37.7/100,000 for males, respectively.[4] In Canada, the national crude incidence rate is reported as 20.75 cases per 100,000 individuals per year.[5] In the United States, melanoma is the fifth most common cancer, with an annual incidence of 73,870 cases.[6] The lifetime risk of developing melanoma has increased dramatically,

Keywords: Age-period-cohort; Oldest-old; Cutaneous malignant melanoma; Incidence; Annual percent change; Incidence trends.

***Correspondence to:** Jun Lyu, Department of Clinical Research, the First Affiliated Hospital of Jinan University, Guangzhou, Guangdong 510630, China. ORCID: https://orcid.org/0000-0002-2237-8771. Tel: +86-13922274169, E-mail: lyujun2020@jnu.edu.cn

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from 1 in 1,500 in the 1930s to 1 in 59 today.[6] CMM, a recalcitrant and aggressive melanocyte malignancy, has demonstrated a conspicuous and continuous rise in incidence globally, drawing significant attention from public health and medical research communities.[7]

Since 1975, the incidence of malignant melanoma in the United States has increased by over 320%, a trend expected to continue until at least 2029.[8] From 2006 to 2017, the United States Hispanic population experienced a particularly rapid increase in melanoma incidence, with Hispanic whites exhibiting the highest incidence of acral lentiginous melanoma compared to other populations of color.[9]

The demographic landscape in the United States is also changing, with an increasing proportion of the population reaching advanced age. By 2050, the population aged 85 years and older is expected to more than double, from 5.7 million to 24 million, making it the fastest-growing demographic.[10] This shift underscores the importance of studying CMM incidence and mortality rates within this age group.[10]

CMM is the leading cause of death among skin tumors, and in recent years, both its incidence and mortality rates have been steadily rising, particularly among the elderly.[11] Older patients with CMM typically present with more aggressive disease characteristics, such as a higher prevalence of ulceration and deeper tumor invasion, as indicated by Breslow's index.[12] These factors often result in a more advanced stage of diagnosis compared to younger patients.[12] Additionally, older adults are more likely to present with melanoma on the head and neck, with lentigo malignant melanoma being more common in this age group.[13,14]

Elderly patients generally have a poorer prognosis, with reduced melanoma-specific survival compared to younger adults.[11] Understanding the differences in clinical presentation and outcomes in the elderly is crucial for optimizing prevention, diagnosis, and treatment strategies tailored to this population.

The Surveillance, Epidemiology, and End Results (SEER) database, maintained by the National Cancer Institute (NCI), is a comprehensive nationwide cancer registry system that aggregates clinical and epidemiological data from cancer patients across the United States. These data are vital for both cancer research and clinical practice, providing researchers with insights into the epidemiological characteristics of various cancers, treatment effectiveness, and patient survival rates.[15,16]

Age-adjusted standardized population rates are essential tools in epidemiological studies and public health assessments. These rates adjust for differences in age distribution across populations, allowing for meaningful comparisons of health outcomes such as disease incidence or mortality. By using a standard population as a reference, these rates offer a more accurate reflection of the true burden of a condition, making them crucial for evaluating health trends, informing policy decisions, and comparing outcomes across different regions or time periods.[17]

In this study, we leverage SEER Research Plus Data from 1987 to 2016, covering eight registries up to November 2021 (1975–2019). We employ an age-period-cohort analysis to explore trends in CMM incidence among the elderly population in the United States. The primary goal is to provide scientific evidence to support the development of strategies for CMM prevention and management in the elderly and to evaluate their efficacy.

The following sections will elaborate on the research methodologies, data analysis, and findings, offering a comprehensive understanding of CMM incidence trends in elderly Americans and the factors influencing these trends.

Materials and methods

The data for this study were obtained from the SEER Program, maintained by the NCI. The SEER database is a comprehensive source of population-based information, covering approximately 34.6% of the United States population. It collects data on cancer incidence, survival, and prevalence from various geographic areas representing a cross-section of the nation. The SEER program is renowned for its high-quality data, gathered from multiple registries across the United States, ensuring a broad and diverse representation of cancer patients.[18,19]

Patient selection

Data from the SEER Program, comprising eight registries, were queried for the period spanning 1987 to 2016. Patients diagnosed with CMM of the skin were identified based on histology using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes 8720/3-8722/3, 8730/3-8780/3, and ICD-O-3 codes C44, C60.9, C63.2. Inclusion criteria were as follows: (1) the primary tumor site was the skin; (2) patients were aged 65 years or older at the time of diagnosis; (3) the diagnosis was confirmed pathologically; (4) complete follow-up data were available, with survival times exceeding zero days; and (5) the diagnosis occurred between 1987 and 2016. Exclusion criteria included: (1) cases where the diagnosis was based solely on autopsy or death certificate information; (2) instances with indeterminate survival times; and (3) patients diagnosed with secondary or metastatic tumors rather than primary CMM.

Statistical analysis

An annual percentage change (APC) analysis was conducted using five-year age intervals and 5-year period intervals, resulting in five age groups (65–69 years, 70–74 years, 75–79 years, 80–84 years, and ≥85 years) and six period intervals (1987–1991, 1992–1996, 1997–2001, 2002–2006, 2007–2011, and 2012–2016). Birth cohorts were defined based on the midpoints of the age and period intervals. Age-adjusted incidence rates were calculated using the United States standard population in 2000. Ratios, with 95% confidence intervals (CIs), were calculated using the Tiwari 2006 revision in SEER*Stat 8.4.2 (NCI).[20]

To assess trends in CMM incidence rates among elderly individuals in the United States from 1987 to 2016, this study used the Joinpoint Regression Model. For population-based trends in cancer incidence and mortality rates, the logarithmic linear model is typically used.

The main outcomes of the Joinpoint model were the APC and the average annual percent change (AAPC), both with their respective 95% CI. In the logarithmic linear model, denoted as $In(y) = \beta_0 + \beta_1 x$, where x represents the year of diagnosis, the APC can be computed using the following formula expressed as follows:

$$APC = \left[\frac{y_{x+1} - y_x}{y_x} \right] * 100 = (e^{\beta_1} - 1) * 100$$

To analyze long-term trends in CMM incidence rates, we used version 5.0 of the Joinpoint program from the NCI, available at https://surveillance.cancer.gov/joinpoint/. This program uses the Monte Carlo permutation method to evaluate the statistical significance of changes in trends. The optimal joinpoint model was determined by analyzing log-transformed data. The APC for individual linear segments and the AAPC for each joinpoint model across the entire study period were calculated, with 95% CI determined using the normal approximation method.[21]

Table 1. Change in cutaneous malignant melanoma incidence rates over time

Variable	Rate (95% CI)		Rate ratio (95% CI)
	1987–1991	2012–2016	
Overall	0.36 (0.35–0.37)	0.99 (0.98–1.01)	2.8 (2.7–2.9)
Sex			
Male	0.52 (0.50–0.55)	1.53 (1.50–1.56)	2.9 (2.8–3.0)
Female	0.25 (0.24–0.27)	0.59 (0.57–0.60)	2.3 (2.2–2.4)
Race			
White	0.40 (0.39–0.42)	1.22 (1,20–1.24)	3.0 (2.9–3.1)
Black	0.07 (0.05–0.11)	0.04 (0.03–0.06)	0.6 (0.4–1.0)
Other	0.04 (0.02–0.05)	0.08 (0.07–0.10)	2.3 (1.5–3.8)
SEER registry			
San Francisco, California	0.385 (0.359–0.413)	1.032 (0.996–1.069)	2.7 (2.5–2.9)
Connecticut	0.398 (0.371–0.425)	0.866 (0.831–0.902)	2.2 (2.0–2.4)
Hawaii	0.228 (0.189–0.272)	0.793 (0.741–0.847)	3.5 (2.8–4.2)
Lowa	0.309 (0.286–0.334)	0.865 (0.828–0.903)	2.8 (2.6–3.1)
New Mexico	0.396 (0.352–0.444)	0.649 (0.609–0.691)	1.6 (1.4–1.9)
Seattle (Puget Sound)	0.345 (0.318–0.373)	1.110 (1.073–1.147)	3.2 (3.0–3.5)
Utah	0.413 (0.366–0.463)	1.506 (1.442–1.571)	3.6 (3.2–4.1)
Atlanta (Metropolitan)	0.385 (0.342–0.431)	1.100 (1.050–1.153)	2.9 (2.5–3.2)

CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

In cases where a significant difference in the linear slope of the time trend was detected, the joinpoint model was used to determine whether the age-adjusted incidence rates were best described by a single linear segment or multiple segments. A statistically significant trend, indicated by the APC or AAPC, was classified as increasing (slope > 0) or decreasing (slope < 0). Parallelism tests were conducted to determine whether the direction of slope changes in trends was similar or different between groups. These tests allowed for an analysis of whether the fitted models for different groups (e.g., females and males) had similar shapes but were shifted along the x-axis (i.e., the year of diagnosis). The statistical significance (*P*-value) from this test indicated whether the two compared AAPCs were statistically distinct.[22] All tests were two-sided, with a significance level set at $\alpha = 0.05$.

Finally, the APC model was employed to identify patterns in long-term incidence rate trends, considering the age at CMM diagnosis (age), the year of CMM diagnosis (period), and the birth year (cohort). The APC model described associations between cancer incidence rates and age, period (calendar year of diagnosis), and birth cohort. Graphs generated from these models provided a visual representation of trends while controlling for competing effects, such as birth cohort influences that adjust for age and period effects. These models were fitted using the NCI's Age-Period-Cohort web tool, available at https://analysistools.cancer.gov/apc/. This tool provided estimates of net drift (the expected age-adjusted rate of change over time in the APC), local drift (the expected age-specific rate of change over time), and cohort rate ratios (RR, the ratio of age-specific rates for each birth cohort relative to a reference cohort). The tool also enabled the testing of the equality of observed trends.[23]

Results

Incidence rates

The study included a total of 56,997 cases, with 36,726 (64.4%) being male patients. During the period from 2012 to 2016, the overall age-adjusted incidence rate of CMM was 0.99 per 1,000 individuals (95% CI, 0.98–1.01), representing a striking 2.8-fold increase compared to the period from 1987 to 1991 (95% CI, 2.7–2.9), as shown in Table 1. When stratified by gender, the age-adjusted incidence rate for males during 2012–2016 was 1.53 per 1,000 (95% CI, 1.50–1.56), while for females, it was 0.59 per 1,000 (95% CI, 0.57–0.60). These findings highlight a significant increase since the initial cohort analysis (1987–1991), with the age-adjusted incidence rate for males rising 2.9 times (95% CI, 2.8–3.0), and for females increasing 2.3 times (95% CI, 2.2–2.4). Additionally, we examined the distribution of CMM incidence rates based on race/ethnicity and geographic location (Table 1). It is evident that CMM is more prevalent in the white population compared to black and other racial/ethnic groups. Among white individuals, the incidence rate of CMM escalated from 0.40 per 1,000 to 1.22 per 1,000 (rate ratio 3.0; 95% CI, 2.9–3.1) between 1987–1991 and 2012–2016. When stratified by geographic location, Utah, Seattle, and Atlanta reported higher CMM incidence rates (Utah: 1.506 per 1,000; 95% CI, 1.442–1.571; Seattle: 1.110 per 1,000; 95% CI, 1.073–1.147), and Atlanta (1.100 per 1,000; 95% CI, 1.050–1.153). The overall increase in incidence rates from 1987–1991 to 2012–2016 was 2.8 times (95% CI, 2.7–2.9).

APC analysis

Over the course of 30 years, from 1987 to 2016, a persistent upward trend in the incidence rate of CMM was observed. Based on the APC, this ascending trend can be divided into two distinct seg-

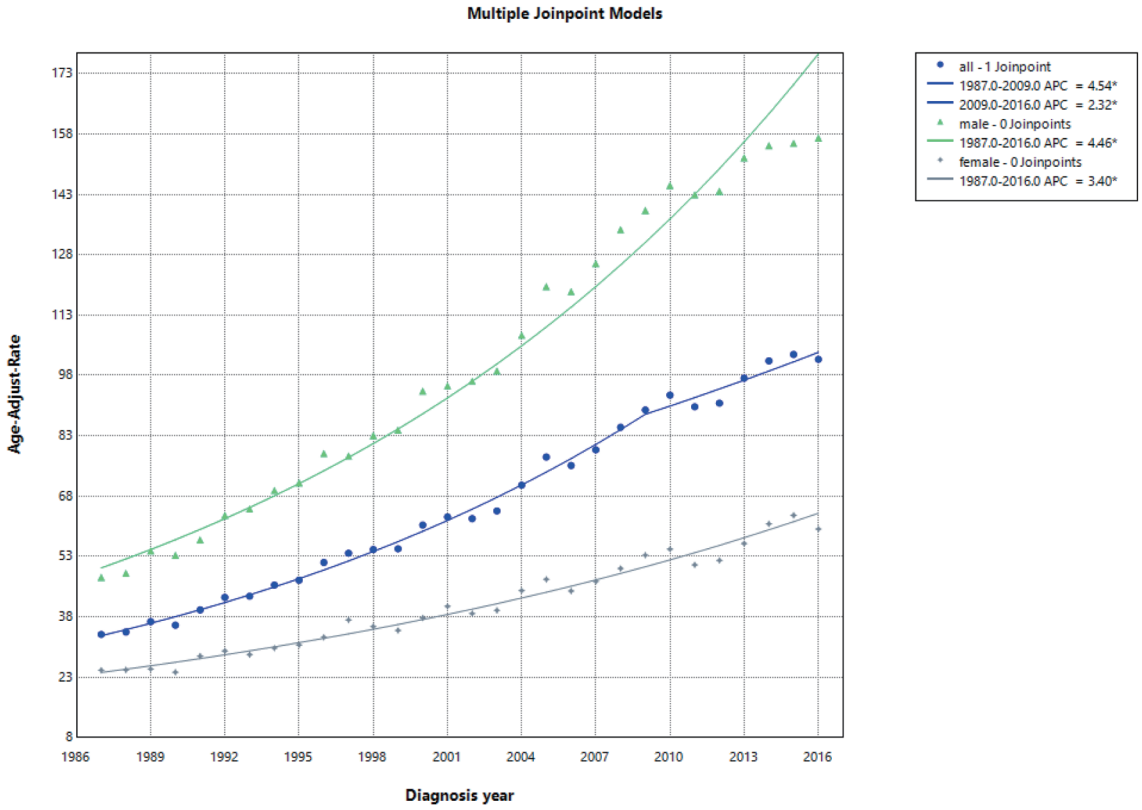

Fig. 1. Associations of age and calendar period of diagnosis with CMM incidence among all patients. CMM, cutaneous malignant melanoma.

ments, with a pivotal shift in 2009. Between 1987 and 2009, there was a pronounced upward trend, with a substantial APC of 4.45%. However, after 2009, the trend moderated, displaying a somewhat less steep incline compared to the earlier period (Fig. 1).

Period trends in age-adjusted CMM incidence rates

We began our analysis by examining the period trends in the evolving incidence rates of CMM in the United States. Figures 2a and b illustrate the fluctuations in age-specific CMM incidence rates across various observation periods (years) for American males and females from 1987 to 2016. Overall, CMM incidence rates tend to be higher in older age groups, regardless of the observation period. Across all five age groups, an upward trajectory in CMM incidence rates is evident over the years. Notably, the 80–84 age group among males exhibits a significantly pronounced upward trend, with an APC of 6.04%. Among females, the 75–79 age group shows a significant upward trend, with an APC of 3.69%. In the male population, the incidence rate of CMM in the 85+ age group initially declines, followed by an increase, with an inflection point in 1989. In contrast, the incidence rate in the 80–84 age group initially rises rapidly but decelerates post-2010, with an APC of 0.31%. Among females, the 75–79 age group shows an initial decline followed by an increase in CMM incidence rates, with the inflection point occurring in 1990.

Cohort trends in age-adjusted CMM incidence rates

Figures 3a and b provide insights into the fluctuations in age-specific CMM incidence rates based on birth cohorts for American males and females from 1987 to 2016. The results from the birth cohort models reveal that, particularly among males aged 65 and older, individuals of the same age but from different birth years show a gradual increase in CMM incidence rates as their birth years advance. In contrast, the differences in birth cohort trends were less pronounced between females and males. CMM incidence rates across various age groups generally show a gradual increase as birth years progress. However, in the elderly male population, the overall incidence rate of CMM exceeded that of elderly females. Notably, male CMM incidence rates, spanning different age groups and birth cohorts, surpassed 44, with males aged 85 and older showing the highest incidence rates.

Age-period-cohort models

As shown by the longitudinal age curve in Figure 4, the incidence rate of skin melanoma peaks in the older age groups. Figure 5a illustrates the rising trend over time, with a notable increase starting around 2000. Rates exceeding 1.0 after 2000 indicate that the incidence of CMM is increasing during these periods compared to the reference period. The shaded areas represent confidence intervals, highlighting a significant upward trend over time. Figure 5b demonstrates a steady rise in incidence rates among recent birth cohorts, indicating that individuals born more recently are at a higher risk of developing CMM than those from earlier cohorts. This increase is particularly sharp for cohorts born after 1940, with a pronounced risk for those born after 1950.

Discussion

The incidence rate of CMM among elderly individuals in the Unit-

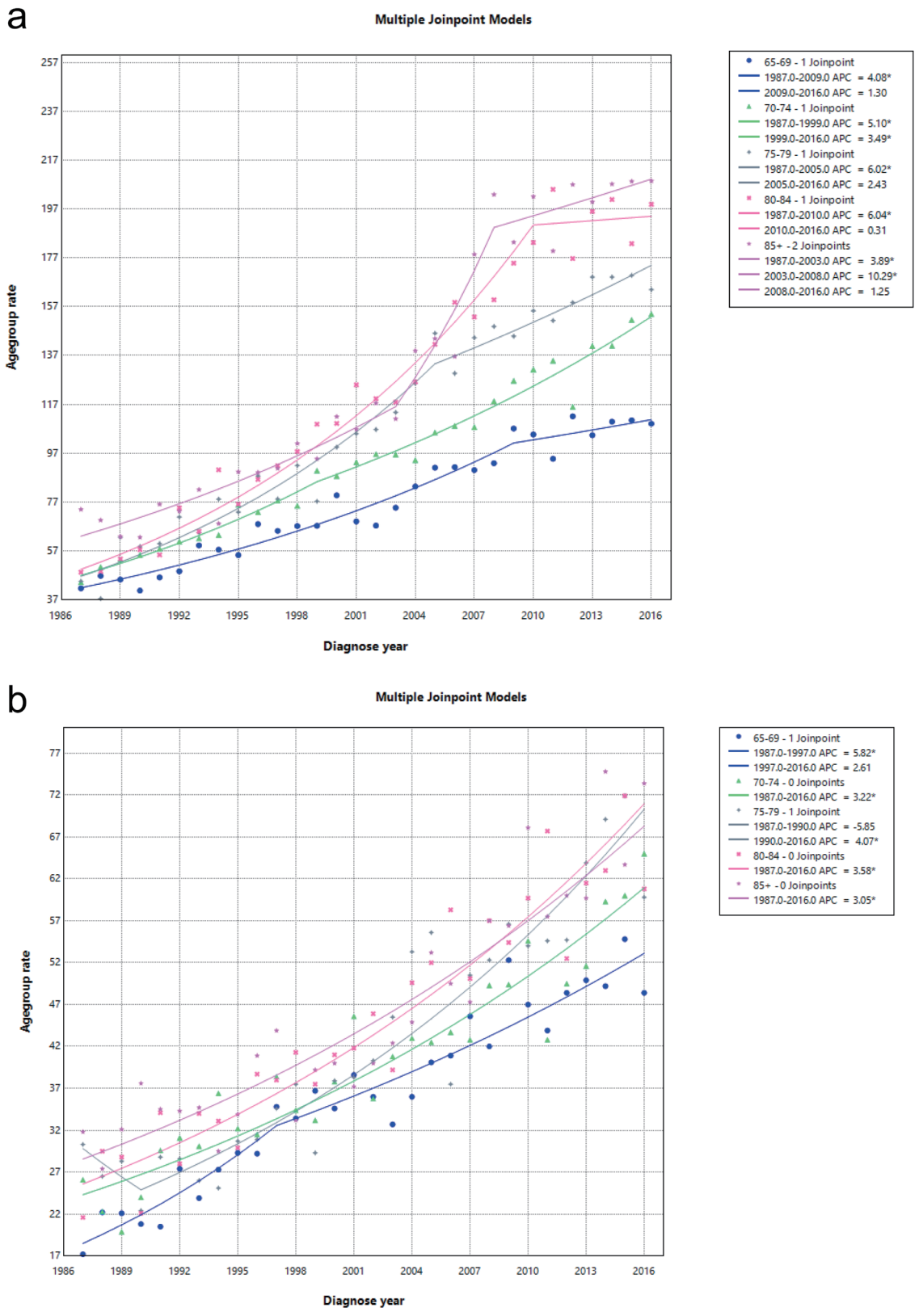

Fig. 2. Associations of age and period of diagnosis with CMM (cutaneous malignant melanoma). (a) Association of age and calendar period of diagnosis with CMM incidence among male patients. (b) Association of age and calendar period of diagnosis with CMM incidence among female patients.

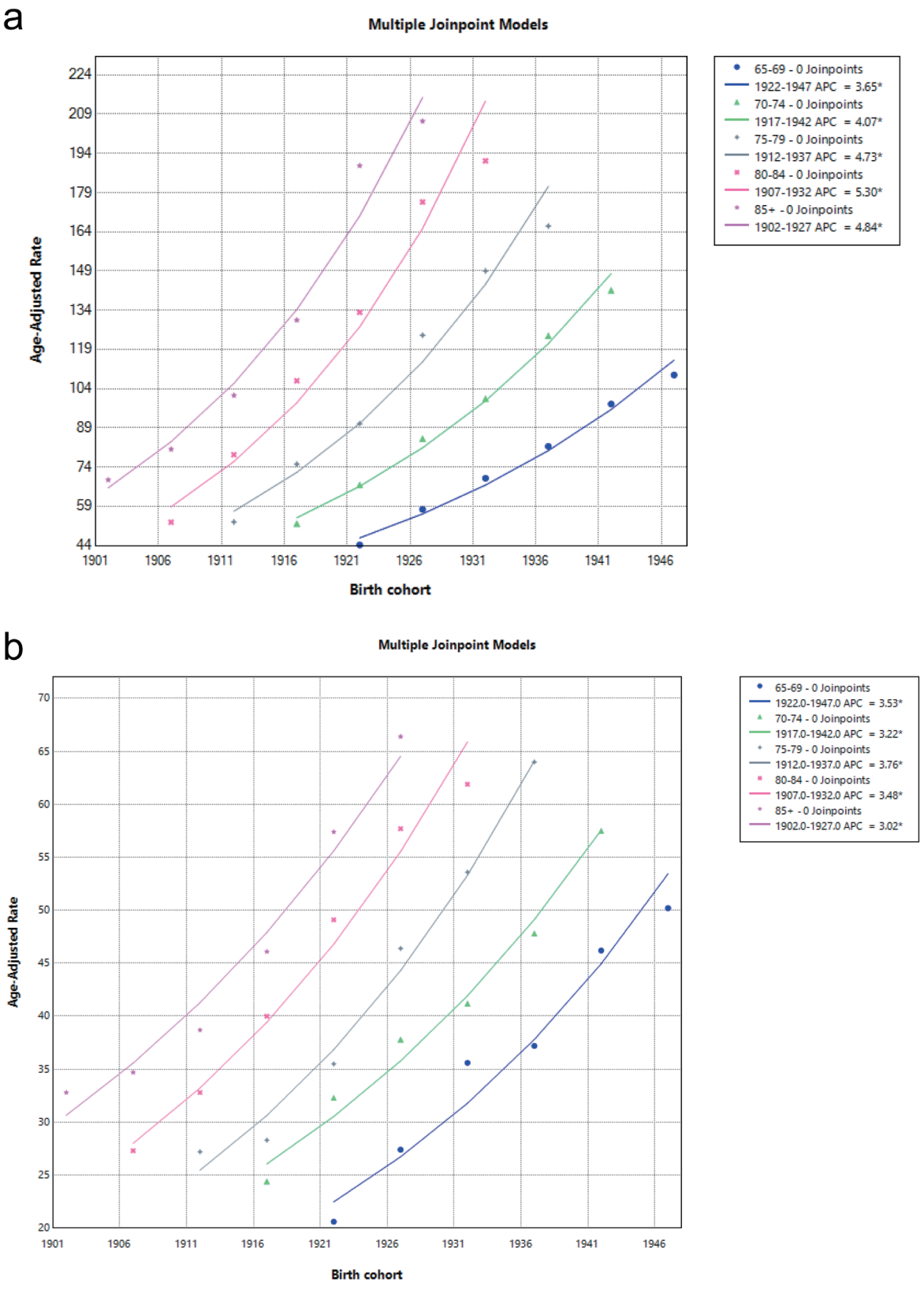

Fig. 3. Associations of age and birth cohort with CMM (cutaneous malignant melanoma). (a) Association of age and birth cohort with CMM incidence among male patients. (b) Association of age and birth cohort with CMM incidence among female patients.

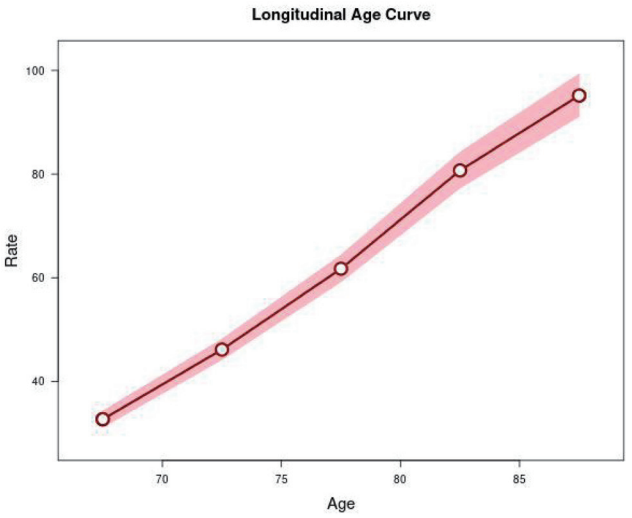

Fig. 4. Longitudinal age curves of CMM in SEER 8 from 1978 to 2016 and corresponding 95% CI. CI, confidence interval; CMM, cutaneous malignant melanoma; SEER, Surveillance, Epidemiology, and End Results.

ed States varies significantly across different genders, races, and geographic locations. Utah had the highest incidence of CMM in older adults from 2012 to 2016 (95% CI, 1.442–1.571). Both Hawaii and Utah show a high rate of increase in CMM incidence. In 2019, Utah had the highest incidence of distant melanoma among white women, with an incidence rate of 3.45 cases per 100,000.[24] This high incidence aligns with broader trends in the United States, where melanoma incidence has been rising, particularly among older adults.[25] The high prevalence in Hawaii and Utah may be related to lifestyle factors that increase Ultraviolet (UV) exposure, such as outdoor activities and tanning habits.[8] Changes in clothing styles and recreational behaviors over recent decades have also contributed to increased UV exposure, particularly in sunny states such as Hawaii.[26] A comparative analysis across different time periods reveals a notable upward trend in overall incidence rates in recent decades.

Utilizing Joinpoint regression to provide a detailed description and statistical analysis of temporal trends in CMM incidence rates among elderly individuals in the United States, this study uncovers a sustained upward trend in CMM incidence over the past three decades. Various factors may contribute to this trend, including prolonged exposure to ultraviolet radiation, indoor tanning, immunosuppression, the presence of moles (nevi), family history, and obesity.[8] This trend is also partly driven by an aging population in industrialized countries, where older individuals are more susceptible to melanoma due to cumulative sun exposure over their lifetimes.[12] A global study analyzing trends from 1990 to 2019 found that the age-standardized incidence rate of malignant skin melanoma increased in most countries, with a positive correlation between incidence rates and the Human Development Index.[27] In the United States, the incidence of melanoma in the lower limbs and hips increased significantly from 2000 to 2019, particularly among those over 50 years old, highlighting a rising trend in older age groups.[28] While the incidence of CMM in the elderly has risen rapidly, the rate of change has slowed since 2010. The inflection point in 2009 suggests that certain factors or interventions may have started impacting melanoma incidence trends after that year. Distinct trends in incidence rates were observed among different male age groups, with the 2009 inflection point, as seen in a melanoma epidemiology study in Hungary, signaling a potential shift influenced by various factors or interventions.[29] The slowdown in malignant melanoma incidence among older adults around 2010 can be attributed to changes in diagnostic practices, healthcare utilization, and demographic shifts. These factors have influenced the detection and management of melanoma in the elderly, potentially stabilizing incidence rates. This suggests that the rise in melanoma incidence prior to 2010 may partly reflect overdiagnosis rather than a genuine increase in disease prevalence. During this period, healthcare utilization increased, including more frequent dermatology visits and skin biopsies for Medicare beneficiaries. This enhanced surveillance may have led to the detection of more early melanomas, many of which do not progress to invasive disease. The stabilization of incidence rates in older adults may indicate efforts to address overdiagnosis, as the detection of non-invasive melanomas has increased without a corresponding rise in mortality, suggesting that many detected cases may not require aggressive treatment.[30]

After adjusting for age, the incidence of CMM exhibited an in-

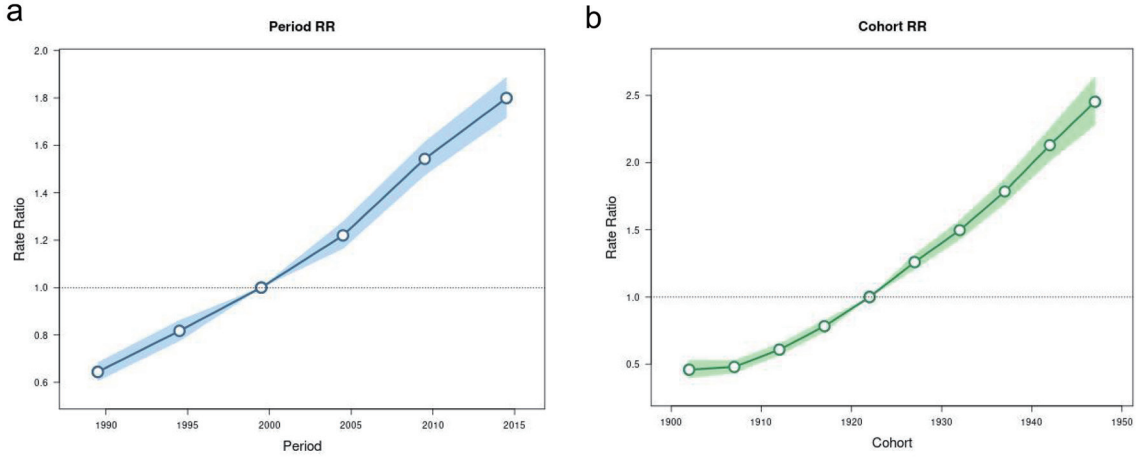

Fig. 5. Incidence rate ratios by period for CMM incidence in SEER 8 (a). Incidence rate ratios by birth cohort for CMM incidence in SEER 8 database (b). Shaded bands indicate the 95% CI. CI, confidence interval; CMM, cutaneous malignant melanoma; RR, rate ratio; SEER, Surveillance, Epidemiology, and End Results.

creasing trend over the observation period. However, in some age groups, notably the 80–84 age group, the growth rate of incidence slowed during a specific period. Incidence rates in elderly females were lower than in elderly males, and overall, the rate of increase in incidence among elderly females was less pronounced than among males. Studies by Bellenghi *et al*.[31] suggest that differences in incidence rates can be partially attributed to gender-related behaviors. Additionally, melanoma incidence in older men exceeds that of women, possibly due to lower rates of skin self-examination and fewer dermatologic visits among men.[32] Furthermore, in the elderly population, melanoma is more frequently located in the head and neck area, with specific subtypes such as lentigo malignant melanoma being more common, along with a higher Breslow index, presence of ulceration, and increased mitotic rate compared to younger individuals.[13] Recent findings indicate that biological variations, including genetic and epigenetic factors, play a crucial role. In recent years, the rate of incidence growth has decelerated, potentially reflecting increased awareness of skin health, more stringent sun protection measures, or improved early detection.[7]

CMM remains a substantial health concern, and according to other research, the number of cases of cutaneous malignant melanoma in the elderly population is expected to rise.[33] These findings underscore the continued importance of vigilance regarding CMM among the elderly and the necessity for prevention and early detection strategies. Age, time period, and birth cohort effects are all critical factors in comprehending the heightened incidence of CMM.

While this study provides valuable insights into the trends in CMM incidence among the elderly in the United States, several limitations must be acknowledged. First, the study relies on data that may be subject to reporting biases, particularly regarding the accuracy and completeness of melanoma diagnoses over time. Second, while Joinpoint analysis offers a robust method for identifying temporal trends, it does not account for potential confounding variables that might influence these trends, such as changes in public awareness, diagnostic technologies, or healthcare access. Third, the study does not differentiate between various histopathological subtypes of CMM, which could have different etiologies and prognoses, potentially leading to an oversimplification of the observed trends. Fourth, geographic variations in sun exposure, socioeconomic factors, and healthcare infrastructure across the United States may not be fully captured in the analysis, limiting the generalizability of the findings. Lastly, the observational nature of this study precludes the establishment of causal relationships between the identified trends and specific risk factors or interventions. Future research should address these limitations by incorporating more granular data, exploring the impact of specific interventions, and utilizing more sophisticated statistical techniques to account for potential confounders.

Conclusions

The incidence of CMM among the elderly population in the United States has shown a notable upward trend over the past three decades. This increase is influenced by a complex interplay of factors, including UV exposure, changes in healthcare practices, and demographic shifts. While the incidence rate continues to rise, particularly in certain geographic regions, there has been a recent deceleration in this trend, possibly due to increased awareness, early detection, and the potential impact of overdiagnosis. Despite this, CMM remains a significant health concern, especially among older adults, necessitating continued efforts in prevention, early diagnosis, and research into targeted interventions. Addressing the limitations identified in this study will be crucial for advancing our understanding of CMM trends and for developing more effective public health strategies to mitigate the burden of melanoma in the aging population.

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Conflict of interest

Jun Lyu is an editorial board member of *Cancer Screening and Prevention*. The authors report no other competing interests.

Author contributions

Conception and design (RFD), data collection and assembly (RFD, JYG), data analysis and interpretation, manuscript writing, and final approval of manuscript (RFD, JYG, JL, JLY). All authors have approved the final version and publication of the manuscript.

Ethical statement

We signed the "Surveillance, Epidemiology, and End Results Program Data-Use Agreement" in accordance with the requirements for using the Surveillance, Epidemiology, and End Results (SEER) database. Therefore, we obtained the data with permission and were able to download it from the SEER database. This article does not fall within the scope of ethics committee review and, according to current ethical standards, does not require ethical approval. The data used in this paper were collected from public databases and are considered public resources.

Data sharing statement

All data generated or analyzed during this study are included in this published article and its supplementary information files. All related information was derived from the SEER program using SEER*Stat version 8.4.1 (https://seer.cancer.gov/).

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