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Global Burden and Trends of Cutaneous Malignant Melanoma in the Elderly Population: Analysis of Global Burden of Disease Study 2021

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Background: Cutaneous malignant melanoma (CMM) represents a substantial health burden for the elderly; however, data regarding its impact and epidemiology within this demographic remain scarce. This study aims to evaluate the global, regional, and national trends of CMM among individuals aged 60 and elderly from 1990 to 2021.

Methods: We retrieved data on the age-standardized incidence, prevalence, and mortality rates, and disability-adjusted life years (DALYs) of CMM among individuals aged 60 and above across 204 countries and territories from 1990 to 2021, sourced from the Global Burden of Disease (GBD), Injuries, and Risk Factors Study 2021. We calculated the estimated annual percentage changes in age-standardized incidence and DALY rates of CMM, categorized by age, sex, and socio-demographic index (SDI), to quantify temporal trends. Additionally, we employed Spearman correlation analysis to examine the relationship between age-standardized rates and SDI.

Results: This study analyzed global trends in CMM from 1990 to 2021 using the GBD database. The findings indicate a significant increase in the incidence (EAPC=0.65, 95% CI: 0.33–0.96) and prevalence (EAPC=1.02, 95% CI: 0.64–1.41) of CMM, while a significant decreasing trend was observed for mortality (EAPC=−0.43, 95% CI: −0.57- −0.30) and DALYs (EAPC=−0.67, 95% CI: −0.82- −0.53). In 2021, high-income North America exhibited the highest prevalence of CMM but the lowest growth rate. In contrast, the Middle East and North Africa experienced the fastest growth rate, while Latin America also demonstrated a significant increase in prevalence. The growth rates of incidence and prevalence were notably higher among male patients compared to females, reflecting gender-specific behavioral differences. Furthermore, an analysis of the relationship between the burden of disease and the SDI for CMM across various regions from 1990 to 2021 revealed that the burden of disease in Australia significantly exceeded model predictions. The APC analysis indicated that the prevalence of CMM among elder population (≥60 years old) declined with age, but the overall disease burden continues to rise annually, demonstrating higher prevalence rates in later birth cohorts. Similar trends were observed for incidence, DALYs, and mortality.

Conclusion: This study reveals that the burden of CMM disease is rapidly increasing among populations residing at lower latitudes. The findings underscore the necessity for dynamic optimization of global prevention and control strategies, considering regional disparities.

Keywords: cutaneous malignant melanoma, elderly population, global burden of disease, sociodemographic index, average annual percent change

Introduction

Cutaneous malignant melanoma (CMM) is a malignant tumor that originates from melanocytes and represents the most lethal type of skin cancer.[1] Although its incidence is relatively low compared to other skin cancers, such as squamous cell carcinoma and basal cell carcinoma, CMM is highly aggressive, accounting for more than 90% of skin cancer-related

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deaths and posing a severe threat to human life and health.[2] In 2020, there were an estimated 325,000 new cases and 57,000 deaths globally. If the incidence rate continues to rise, it is projected that by 2040, there will be an estimated 510,000 new cases and 96,000 deaths annually.[3]

With the global population continuing to age, health issues related to the elderly have garnered significant attention. In clinical research, elderly adults with cancer are commonly defined as those aged 60 years or elderly.[4] It has been reported that age is a very strong independent risk factor affecting the prognosis of patients with CMM. Compared to other age groups, elderly patients with CMM exhibit significantly higher mortality rates, as they demonstrate the most aggressive prognostic features of primary melanoma, including deeper invasion, higher mitotic rates, and a greater likelihood of ulceration.[5–7] Furthermore, elderly patients with CMM face numerous challenges, including delayed diagnosis, multiple comorbidities, declining nutritional and immune functions, significant psychological and emotional stress, and poor treatment tolerance.[8–10] These factors have adversely impacted the diagnosis, treatment, and prognosis of elderly patients with CMM.

While recent studies based on the Global Burden of Disease (GBD) have characterized the global burden of CMM,[11,12] there remains a need for a focused analysis specifically targeting the elderly population. Such an analysis should examine the most recent trends and their specific drivers to inform targeted public health and clinical strategies for this high-risk group. Our analysis conducts a more refined examination of the disease burden and trends in the elderly population, focusing specifically on age stratifications, temporal trends, and previously underemphasized comparative analyses. It is crucial for countries and health organizations worldwide to conduct extensive examinations of the impact of CMM on the elderly to develop targeted public health strategies and achieve health objectives.

In this study, we performed a secondary data analysis utilizing the results of the GBD 2021, gathering comprehensive information on incidence, mortality, and disability-adjusted life years (DALYs) at global, regional, and national levels. We employed Joinpoint and Age-Period-Cohort (APC) models to rigorously analyze and interpret the epidemiological trends observed over the past three decades. The findings of this study significantly enhance the existing epidemiological evidence on CMM among elderly patients and provide a crucial foundation for formulating and refining public health policies aimed at addressing this critical health issue.

Materials and Methods

Study Population and Data Collection

The GBD study, conducted by the Institute for Health Metrics and Evaluation (IHME), provides comprehensive and comparable metrics of global health. The data utilized in this study are derived from the GBD 2021 dataset repository as of March 15, 2024, offering critical insights into mortality rates, disease burdens, and risk factors across various regions and populations. The data were accessed and downloaded using the GBD Results Tool, which is publicly available at [GBD Results Tool] (https://vizhub.healthdata.org/gbd-results/). This dataset serves as an integrated database that records the incidence, prevalence, and mortality for 369 diseases and injuries across 204 countries and territories, classified by age and gender. The study extracted and analyzed data on the age-standardized incidence, prevalence, case-fatality rates, and DALYs of CMM from 1990 to 2021 globally, segmented by gender. In alignment with the GBD standard age grouping and to ensure a comprehensive analysis of the elderly population, we utilized the following age strata: 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, and 90–95 years. All estimates for the broader category of "60 years and above" were calculated by aggregating data from these specific age groups.

GBD 2021 Estimation Methodology for CMM

The estimates for the burden of CMM were derived from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021. Case data were collated from population-based cancer registries, vital registration systems, and scientific literature. Cases were identified based on diagnosis and coded according to the International Classification of Diseases (ICD), primarily utilizing ICD-10 code C43, which pertains to malignant melanoma of the skin. Mortality data were processed from cause-of-death records using the same ICD code. The estimation process employed the standardized modeling tools provided by the GBD. Specifically, the disease modeling software DisMod-MR 2.1 was utilized as a Bayesian meta-regression tool to synthesize all available incidence, prevalence, and mortality data. This approach

ensured epidemiological consistency and facilitated the generation of estimates for regions with missing data. Subsequently, the CodCorrect algorithm was applied to guarantee that cause-specific mortality estimates summed accurately to the total all-cause mortality figures. All estimates are presented alongside their 95% uncertainty intervals, which reflect the robustness of both the data and the model.

Statistical Analysis

This study extracted data from the GBD database regarding the incidence, prevalence, mortality rate, DALYs, and the corresponding age-standardized rates: age-standardized incidence rate (ASIR), age-standardized prevalence rate (ASPR), age-standardized mortality rate (ASMR), and age-standardized disability-adjusted life rate (ASDR) for elderly patients with CMM globally. We used the Joinpoint software (version 4.9.1.0, https://surveillance. cancer. gov/joinpoint/) developed by the National Cancer Institute Division of Cancer Control & Population Sciences. The Monte Carlo permutation test, the default model optimization method of the Joinpoint software, was used to select the optimal number of joinpoints. All models were fitted with a maximum of 5 joinpoints, corresponding to 6-line segments. This parameter was selected to balance model flexibility and parsimony while effectively capturing meaningful trend transitions. The same maximum joinpoint limit (5 joinpoints) and permutation test criteria were uniformly applied across all stratification levels, including global, regional, anatomical subsite, and sex-specific analyses. For data series with fewer than eight observed data points, the software's internal algorithm automatically constrained the maximum number of joinpoints to prevent overfitting. The Joinpoint software was utilized to calculate the estimated annual percentage change (EAPC) and the associated 95% confidence interval (95% CI) to assess trends in disease burden. The logarithmic age-standardized indicators were fitted into the regression model represented by $\ln(y) = \alpha + \beta x + \varepsilon$, where y denotes the respective age-standardized indicators and x signifies the calendar year. The EAPC is calculated as $(e^{\beta} - 1) \times 100$, with the 95% CI derivable from the model. An EAPC estimate with a 95% CI greater than 0 indicates an upward trend in the age-standardized indicator, while a CI less than 0 indicates a downward trend; if the CI includes 0, it suggests a stable trend.

We conducted the analyses using the age-period-cohort Web Tool developed by the National Cancer Institute, which employs a statistical approach based on weighted least squares. This method operates under the fundamental assumption that the count data follows Poisson distribution. To address the identifiability issues associated with the age-period-cohort model, the Web Tool represents the model using estimable functions that relate to the parameters of age, period, and cohort, in accordance with Holford's Age-period-cohort (APC) model. An APC model was fitted to the ASIR data to disentangle the underlying age, period, and birth cohort effects. The model estimated the net drift (the overall annual percentage change), local drifts (age-specific annual percentage changes), and the relative risks associated with specific age groups, calendar periods, and birth cohorts. The results are presented as coefficients with their 95% confidence intervals. In this model, each set of effects is expressed through linear combinations of curvature effects, allowing for a more nuanced understanding of the data. Additionally, the functions representing the slopes associated with age, period, and cohort effects are estimable, facilitating in-depth analysis. The mathematical equations that underpin this model are detailed below. Typically, the APC model is represented by the equation: $Y = \log(M) = \mu + \alpha(\text{age})i + \beta(\text{period})j + \gamma(\text{cohort})k + \varepsilon$.[13]

In this study, statistical analysis and data visualization were performed using R statistical software (version 4.3.2) and Joinpoint software (version 4.9.1.0).[14–16] We employed the APCtoolkit package (version 0.1.5) in R to fit the APC model. The input data was an age-period matrix of incidence rates. The model outputs, including the net drift, local drifts, and the estimated coefficient for age, period, and cohort effects, were exported from R for result synthesis and the creation of figures and tables. A P-value of less than 0.05 was deemed statistically significant.

Results

Global Burden of Disease and Temporal Trends of CMM,1990-2021

To assess the trends in the GBD related to CMM, we obtained statistical data on global CMM patients from the GBD database for the period between 1990 and 2021. We calculated the incidence, prevalence, deaths, and their respective age-standardized rates (ASR) for CMM. Additionally, the EAPC for these metrics was computed to illustrate the trend of

each relevant statistical value of CMM from 1990 to 2019, as shown in Supplementary Table 1. Based on the statistical data, the EAPC for global average prevalence from 1990 to 2021 was 1.02(95% CI:0.64–1.41), the incidence rate was 0.65(95% CI:0.33–0.96), mortality was −0.43(95% CI:-0.57–0.30), and the EAPC for DALYs was −0.67(95% CI:-0.82–0.53). Overall, it appears that the incidence and prevalence of CMM globally exhibit an increasing trend, while mortality and DALYs show a decreasing trend. In various regions of the world, both the incidence and prevalence cases were predominantly concentrated in high-income North America, which had a relatively high ASR of 133.27 (127.26–137.47) per 100,000 (95% UI) in 2021 but recorded the lowest EAPC of −0.06 (−0.51 to −0.39) (95% CI) between 1990 and 2021 compared to the rest of the world. In high-income North America, morbidity exhibited a similar profile, with an ASR of 16.61 (15.75–17.15) per 100,000 (95% UI) for incidence in 2021, accompanied by an EAPC of −0.17 (95% CI: −0.59 to 0.25), indicating a non-significant trend during the period from 1990 to 2021. Conversely, Latin America, characterized by a lower prevalence and incidence, along with Eastern Europe, demonstrated relatively higher incidence and prevalence rates compared to other regions globally. Notably, North Africa and the Middle East recorded the highest EAPC for prevalence at 5.3 (5.11–5.49) (95% CI) and an incidence EAPC of 2.86 (2.78–2.94) (95% CI) during the period from 1990 to 2021. The changes in incidence (0.89(95% CI:0.53–1.24)) and prevalence (1.34(95% CI:0.9–1.79)) were greater in men than in women, who exhibited changes of 0.72(95% CI:0.39–1.06) for prevalence and 0.41(95% CI:0.13–0.69) for incidence. Detailed ASR incidence data for 204 countries and territories are visualized in Figure 1.

To quantitatively validate the observed global geographical pattern, we analyzed the correlation between the absolute latitude of each country's geographic centroid and its ASIR in 2021. This analysis revealed a strong and statistically significant negative correlation (Spearman's rho = −0.72, 95% CI: −0.78 to −0.65), providing robust statistical evidence that CMM incidence increases significantly at lower latitudes, closer to the equator.

Global Trends by SDI and Gender

We organized the data according to different SDI regions and gender groups to obtain the total incidence, morbidity, and DALYs, along with their respective ASR for various SDI regions (Figure 2) and genders (Figure 3) from 1990 to 2021. The total incidences, prevalence, and DALYs were significantly higher in high SDI regions compared to other SDI regions. The overall prevalence, incidence, and DALYs exhibited an upward trend across all districts (Figure 2A). The ASR for DALYs, prevalence, and incidence in high SDI areas surpassed those in other SDI areas, with both prevalence and incidence generally increasing until 2010 and subsequently declining thereafter. In medium-high SDI areas, ASR for prevalence and incidence increased gradually between 1990 and 2021, while ASR for DALYs remained relatively stable In the remaining SDI areas, prevalence, incidence, and ASR for DALYs have stabilized at levels significantly lower than those observed in high and medium-high SDI areas (Figure 2B).

Overall prevalence, morbidity and DALYs have increased by gender (Figure 3A). In the different gender subgroups, the ASR for prevalence and incidence exhibit a similar pattern, with both displaying an increase prior to 2010 followed by a decrease thereafter. Notably, the ASR values for the male group are consistently higher than those for the female group. Regarding the ASR of DALYs, both males and females demonstrate a decreasing trend, with the DALY values for males remaining higher than those for females (Figure 3B).

Burden Trends by Gender and Age (60-95+)

By dividing people over 60 years old into groups every five years, presenting their total numbers through bar charts, and their ASR values through line graphs, and differentiating between different genders, Figure 4 visualizes the total number of prevalence, total number of incidences, total number of DALYs, and their respective ASR values and trends in the different populations of people aged 60 years old and above. It illustrates the prevalence, incidence, and DALYs among individuals aged 60 and elderly by categorizing them into five-year age groups. The total counts are represented through bar charts, while the ASR are depicted using line graphs. Additionally, the data distinguishes between genders, providing a comprehensive overview of the trends and variations in these health metrics across different segments of the elderly population. In various populations, both the total number of incidents and the total number of DALYs tended to decrease with increasing age groups. The highest total number of incidents was observed in the 65–69 age group, while the highest

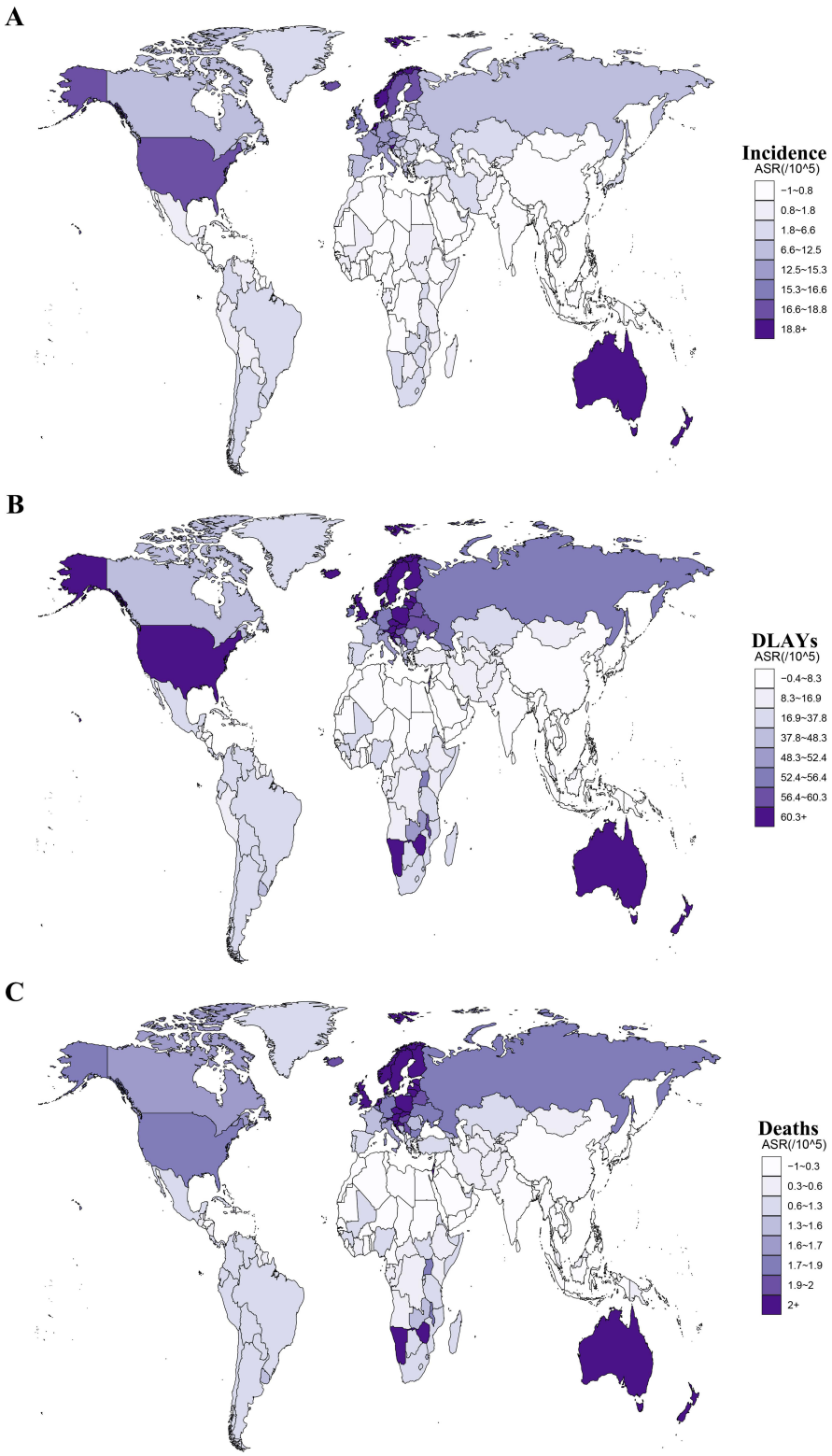

Figure 1 Age-standardized disease burden of CMM across 204 countries and territories from 1990 to 2021. (**A**) ASIR of CMM across 204 countries and territories from 1990 to 2021. (**B**) Age-standardized DALYs of CMM across 204 countries and territories from 1990 to 2021. (**C**) ASDR of CMM across 204 countries and territories from 1990 to 2021.

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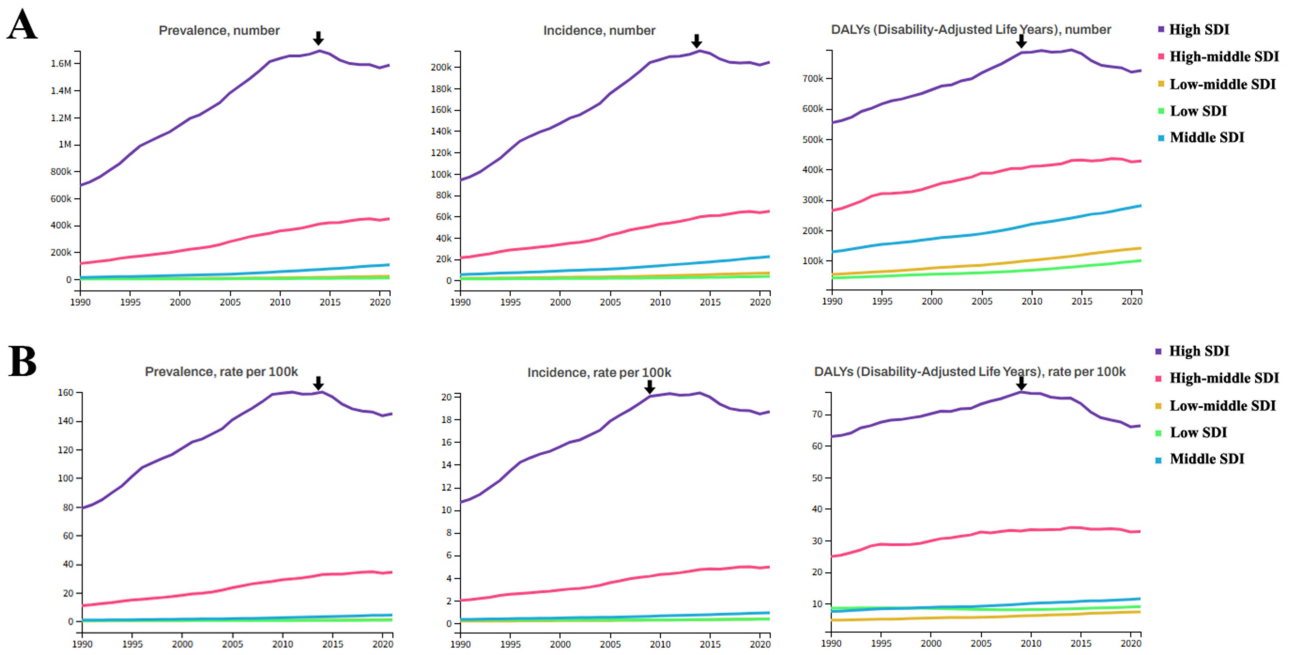

Figure 2 Trends in the disease burden of CMM from 1990 to 2021 by different SDI level regions. (**A**)Trends in prevalence, incidence and DALYs of CMM from 1990 to 2021 by different SDI level regions. (**B**)Trends in ASPR, ASIR and age-standardized DALYs of CMM from 1990 to 2021 by different SDI level regions.

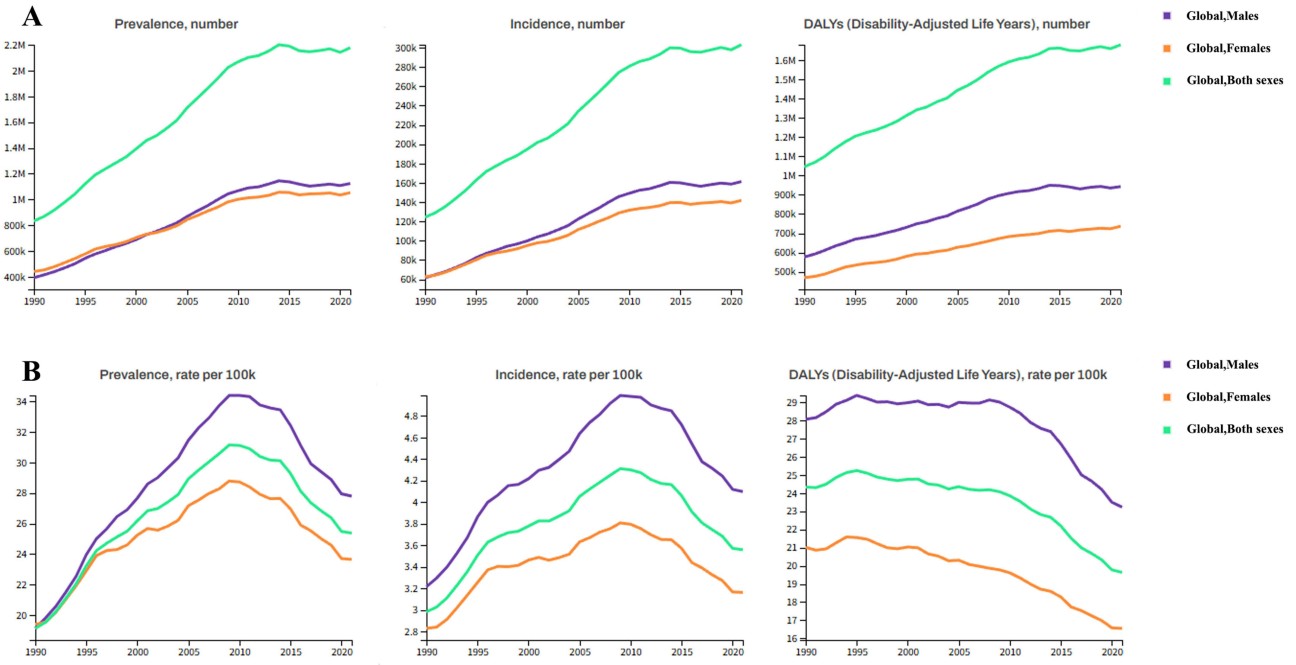

Figure 3 Trends in the disease burden of CMM from 1990 to 2021 by genders. (**A**)Trends in prevalence, incidence and DALYs of CMM from 1990 to 2021 by genders. (**B**)Trends in ASPR, ASIR and age-standardized DALYs of CMM from 1990 to 2021 by genders.

number of deaths occurred in the 75–79 age group. The ASPR exhibited an increasing trend up to the 85–89 age subgroup, reaching its peak at this age before declining rapidly in the subsequent groups. The ASR for the number of incidences displayed a similar pattern until the 85–89 age subgroup, after which gender differences emerged: it remained elevated for males while declining for females. Regarding the ASR for DALYs in the population, it showed an increasing

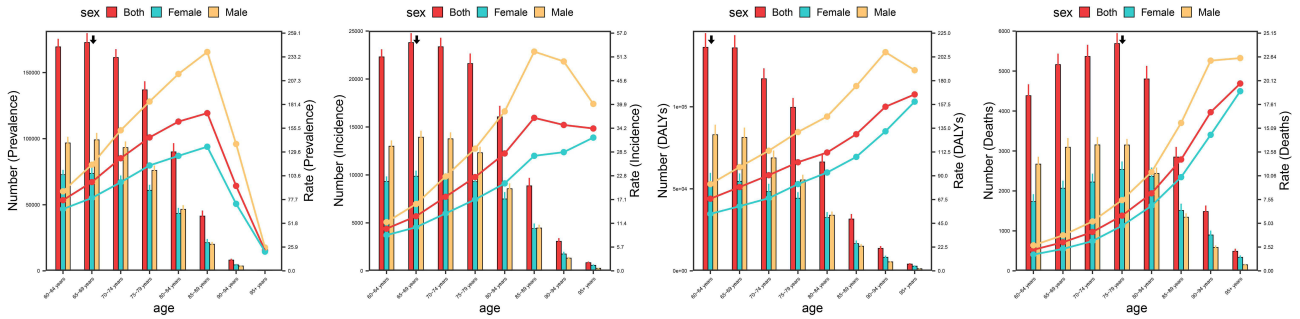

Figure 4 Trends in ASIR, ASDR, ASPR, and DALYs for CMM by genderand age groups, 1990–2021. Arrows indicate the age groups with the highest number of cases during the study period.

trend until the 90–94 age group; beyond this age, it continued to rise for females but declined for males. Similarly, the ASR for the number of deaths in the population maintained an increasing trend until the 90–94 age group, followed by a decline in the male group. In the 95+ age subgroup, the ASR for deaths among males did not increase, whereas the female group continued to demonstrate an upward trend.

The Trends for the Burden of CMM by Main SDI Regions

We collated and analyzed trends in ASPR, ASIR, ASDR, and age-standardized disability-adjusted life years in relation to SDI for CMM from 1990 to 2021, both globally and across the 21 GBD regions. The fitted curves indicate that the relationship between age-standardized burden of disease indicators and SDI varies by region. Notably, the study's results reveal that Australasia's values were significantly higher than those predicted by the fitted curve across all four dimensions when compared to other regions (Figure 5).

The APC Study of CMM

APC model was employed to disentangle the underlying effects on the trends of CMM prevalence, incidence, DALYs, and mortality among the elderly population (Figure 6). The results can be interpreted as follows:

1. Age Effects: The analysis revealed a distinct age effect, where the risk of CMM exhibited a steady increase with advancing age, peaking in the 85–89 age group before declining in the oldest-old population (90+). This pattern aligns with the biological processes of aging and the accumulation of genetic and cellular damage over a lifetime.

2. Period Effects: A significant period effect was observed, marked by a notable upward shift in risk for all age groups beginning around the early 2000s. This trend is likely attributable to period-specific factors, including the widespread adoption of dermoscopy, enhanced skin cancer awareness campaigns, and improved cancer registry completeness, which have collectively led to increased detection and diagnosis across all cohorts.

3. Cohort Effects: The APC analysis also identified a pronounced birth cohort effect. Successive birth cohorts exhibited a higher risk of CMM compared to earlier cohorts. Specifically, cohorts born after the 1940s demonstrated a progressively increasing relative risk. This suggests the influence of evolving behavioral patterns across generations, such as increased recreational sun exposure and tanning habits during youth. Conversely, an attenuation in the rate of increase or a decline in risk was observed for the most recent cohorts (eg, those born after 2000), potentially reflecting the positive impact of public health primary prevention initiatives, such as sunscreen use and sun-protective behaviors.

Sensitivity Analysis

The results of the sensitivity analysis, which stratified the study period into 1990–2005 and 2006–2021, confirmed the robustness of the primary trends. As detailed in Supplementary Table 2, the direction and statistical significance of the EAPCs for incidence, prevalence, mortality, and DALYs remained consistent across both sub-periods. The increasing trends in incidence and prevalence, alongside the decreasing trends in mortality and DALYs, were upheld in both the

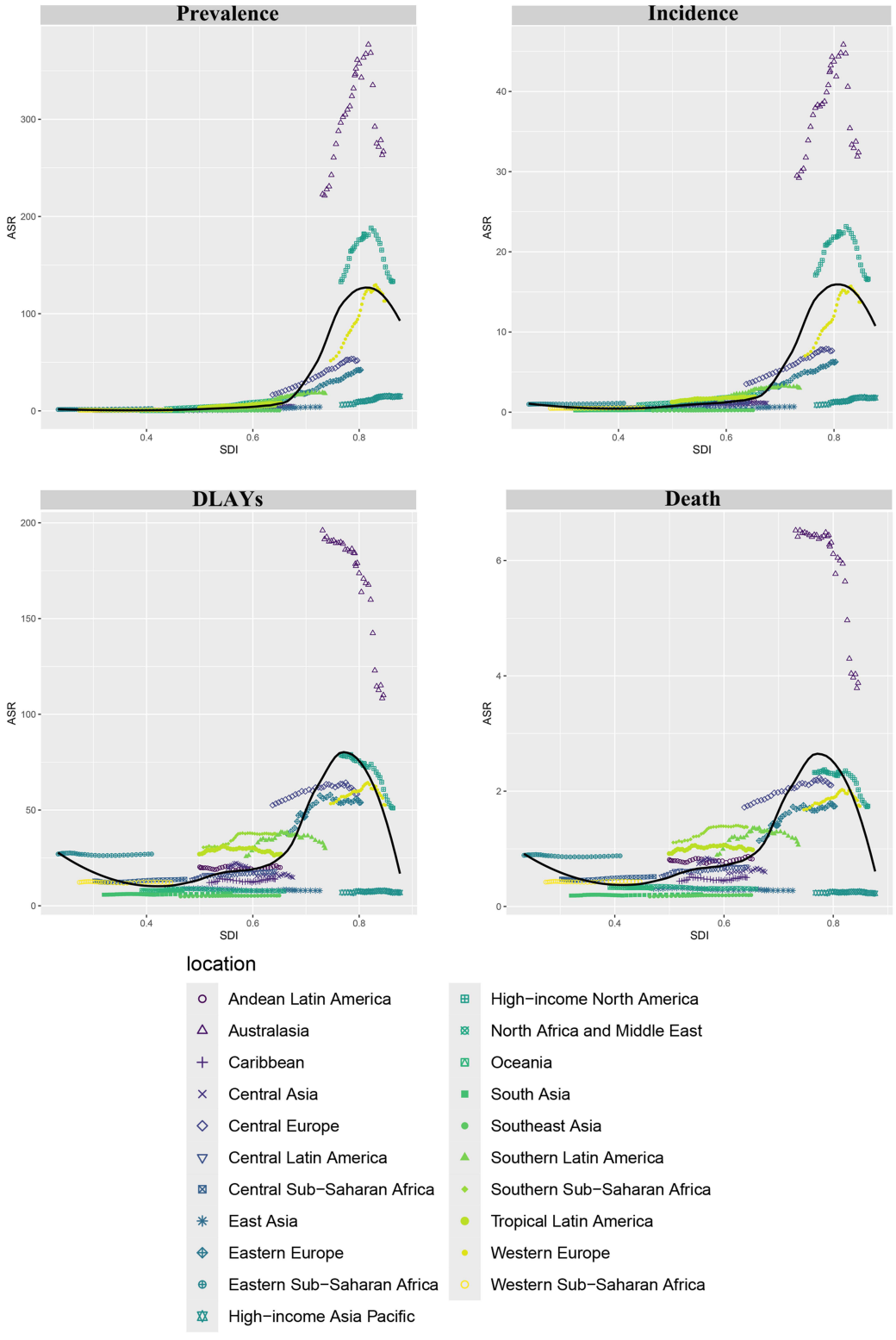

Figure 5 Trends in ASPR, ASIR, ASDR, age-standardized DALYS for the burden of CMM across Global and 21 GBD regions by SDI from 1990 to 2021.

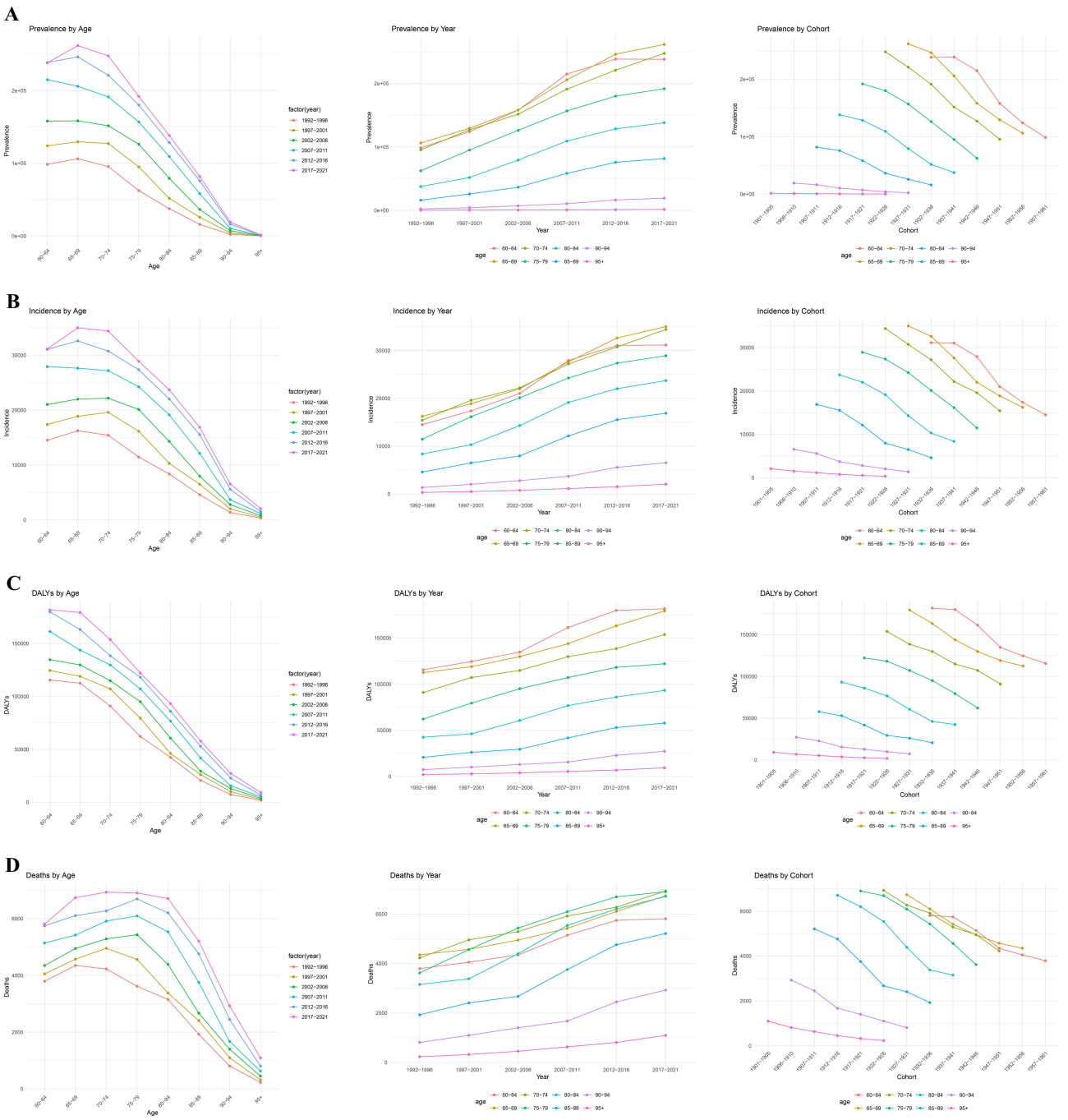

Figure 6 APC Study on prevalence, incidence, DALYs, and deaths of CMM in People Aged 60 to 95+, 1990–2021. (**A**) APC Study on prevalence of CMM in People Aged 60 to 95+. (**B**) APC Study on incidence of CMM in People Aged 60 to 95+. (**C**) APC Study on DALYs of CMM in People Aged 60 to 95+. (**D**) APC Study on death of CMM in People Aged 60 to 95+.

earlier and later halves of the study timeline. This demonstrates that the reported global trends are stable and not unduly influenced by any single segment of the 31-year period.

Discussion

This study focuses on assessing the GBD of CMM among individuals aged 60 years and elderly from 1990 to 2021. It analyzes prevalence, incidence, DALYs, and mortality by SDI region and by sex. Additionally, the APC study is utilized to examine how the prevalence, incidence, DALYs, and mortality of CMM vary across different age groups, years, and

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cohorts within the elderly population. The findings indicate that the global burden of CMM continues to rise, with significant disparities in disease burden observed between regions and countries. A substantial proportion of cases is concentrated in high-income North America, where a decreasing trend in disease burden has been noted. Conversely, increasing trends are evident closer to the equator, particularly in Australasia, Latin America, North Africa, and the Middle East. This phenomenon may be associated with the skin pigmentation of populations in these regions and the levels of UV radiation in their environments. Our study reveals significant disparities in the burden of CMM between regions, with a particularly rapid increase observed in low-latitude areas. Our quantitative latitudinal analysis, demonstrating a strong inverse correlation between latitude and ASIR (Spearman's rho = −0.72, $p < 0.001$), directly links this spatial distribution to proximity to the equator. This phenomenon is most plausibly driven by the corresponding gradient in ambient ultraviolet radiation (UVR), a well-established risk factor for CMM. Research indicates that CMM is a disease influenced by multiple factors, which include both genetic predispositions and environmental elements, with considerable UVR identified as a primary environmental risk factor for its development.[17,18] The intensity of ultraviolet radiation, particularly ultraviolet radiation B(UVB), is significantly higher at low latitudes compared to high latitudes due to the greater angle of incidence of the sun. UVB(290–320 nm) is the primary carcinogenic spectrum, which indirectly contributes to the deterioration of the tumor microenvironment primarily through oxidative stress.[19] The global disease burden of CMM exhibits significant regional and geographic variations. Consequently, it is essential to develop tailored prevention and control policies that account for the variation in disease burden among various regions, focusing specifically on areas at higher risk, like those found in low-latitude zones.

While the absolute number of cases (incidence and prevalence) is rising, the age-standardized rates of mortality and DALYs are declining. This apparent divergence can be explained by the concurrent effects of demographic shifts, advancements in clinical practice, and therapeutic innovation. Firstly, the observed increase in the absolute burden is largely attributable to demographic aging and population growth. The risk of developing CMM increases exponentially with age, and the growing cohort of elderly adults globally inevitably leads to a higher number of total cases, even if age-specific risk remains constant. Secondly, the rise in incidence, particularly of early-stage disease, is fueled by enhanced detection. Improvements in skin cancer awareness, the widespread use of dermatoscopy, and opportunistic screening programs have led to a substantial increase in the diagnosis of thin, localized melanomas. These early-stage cancers have a very high survival rate, meaning they contribute significantly to incidence counts but minimally to mortality statistics. This "stage migration," coupled with debates about potential over-diagnosis, amplifies the incidence trend without a proportional increase in deaths. Finally, and most critically, the significant decline in ASMR and ASDR is a direct testament to remarkable therapeutic advances. The last decade has seen a paradigm shift in the management of advanced melanoma with the advent of immune checkpoint inhibitors and targeted therapies. These treatments have profoundly improved survival outcomes for patients with metastatic disease, thereby directly reducing cause-specific mortality and the associated disability, even in the face of a growing patient population. In conclusion, the rising burden reflects the challenge of an aging world and our success in early detection, while the falling mortality rates celebrate the triumph of modern oncology. This underlines the necessity of sustaining both public health prevention efforts and ensuring equitable access to life-saving treatments.

Our study also found that the burden of CMM varies across regions with different SDI. The risk of developing the disease is higher in populations residing in high SDI regions. This is attributed to certain lifestyle habits prevalent among high-income populations, such as recreational sunbathing and increased outdoor activities, which consequently lead to a higher frequency of exposure to UV radiation.[20] The heightened awareness of CMM among populations in high SDI regions may result in increased screening efforts, subsequently leading to more comprehensive recording and reporting of cases.[21,22] Our study indicates that the burden of disease in high SDI regions has decreased over the past decade. Conversely, we observe an increase in the burden of CMM in other SDI regions, underscoring the urgent need to enhance cancer management strategies beyond high SDI regions.

Our research indicates that men over 60 years old experienced a significantly higher burden of disease compared to women, supporting earlier studies' conclusions.[23] CMM in men is more prevalent in areas such as the trunk, head, and neck exposed to ultraviolet light, which are often challenging for self-examination. Consequently, men are more likely than women to experience delays in seeking medical attention.[24] The five-year survival rate for CMM is significantly

higher in women than in men, with rates of 72.6% compared to 66.8%. Additionally, the recurrence interval is longer in women. Tumors in male patients are more likely to exhibit adverse features, including ulceration and lymph node metastasis.[23,24] All these factors contribute to a higher disease burden in men compared to women in the age group of 60 and above. In addition to these behavioral and healthcare-seeking factors, growing evidence points to underlying biological mechanisms contributing to the sex disparity. Sex hormones are hypothesized to play a role, with estrogen potentially exerting protective effects on melanocytes and modulating immune responses, while androgens might promote more aggressive tumor behavior. Furthermore, inherent sex-based differences in immune function and surveillance may lead to variations in anti-tumor immunity and response to immunotherapy. These biological factors, interacting with behavioral risks, could predispose elderly men to developing melanomas with more adverse prognostic features and contribute to their poorer survival rates independently.[25]

Our findings of an increasing disease burden with advancing age, peaking in the oldest-old subgroups, are not only a reflection of cumulative UV exposure but also a consequence of the complex interplay of age-specific biological and clinical factors. Firstly, comorbidities such as cardiovascular disease, diabetes, and cognitive impairment are highly prevalent in the elderly population. These conditions can complicate the clinical management of CMM by competing for healthcare resources, masking symptoms which lead to delayed diagnosis, and contraindicating certain effective treatments.[8,9,10]

Secondly, treatment tolerance diminishes with age due to the decline in functional reserve of vital organs and altered pharmacokinetics. This often necessitates dose modifications, delays, or even the withholding of standard surgical, adjuvant, or systemic therapies (including innovative immunotherapies), potentially compromising oncological outcomes.[5,7] Furthermore, the aging immune system, a state known as immunosenescence, is characterized by a decline in T-cell function and a chronic, low-grade inflammatory state ("inflammaging"). This has a dual negative impact: it may reduce the body's intrinsic ability to control tumorigenesis, and emerging evidence suggests it might also blunt the response to immune checkpoint inhibitors, which are a cornerstone of modern melanoma treatment. Therefore, the higher burden we observed in the elderly is a multifactorial issue, stemming from a convergence of aggressive tumor biology, patient-level vulnerabilities, and constraints in therapeutic management.

From the APC study of individuals aged 60 years or elderly conducted between 1990 and 2021, we observed a steep increase in the slope of the year curve after 2000. This trend may reflect several factors, including updated diagnostic criteria, the popularization of dermoscopy, and the cumulative effects of environmental exposures. Notably, among the cohort effects, the convexity observed in the cohort curve for individuals born in the 1940s to 1960s may be associated with the post-World War II industrialization process, which accelerated exposure to environmental carcinogens, as well as a period characterized by a gap in sunscreen awareness;[26] The decline of the cohort curve after 2000 supports the elevated SPF values of sunscreens, as broad-spectrum sunscreens have been widely utilized since the 1990s. Additionally, the impact of public health education, exemplified by Australia's Slip-Slop-Slap campaign, further underscores this trend.[27]

Using data from 204 countries and territories, our study reveals significant disparities in the burden of CMM disease between high SDI regions and others, underscoring regional inequalities. Through the APC study, we specifically characterized the burden of CMM across various cohorts from 1990 to 2021, offering critical insights for long-term public health planning. Our findings indicate that public health interventions implemented in certain high-prevalence regions are effective and should be replicated in other areas, particularly in the Middle East, North Africa, and Latin America, where the disease burden is escalating annually. Research in this area has improved our comprehension of the elements that contribute to the burden of CMM, encompassing shifts in demographics, changes in epidemiology, and inequalities within healthcare systems. These findings are crucial for policymakers as they design interventions suited to the specific socio-demographic circumstances of various regions. Furthermore, the study identified significant gender disparities, with higher prevalence, morbidity, and mortality rates observed among men aged 60 years and elderly. This highlights the necessity for male-specific public health strategies, including targeted screening campaigns, promotion of effective preventive measures, and raising awareness among men regarding CMM to address risk behaviors and healthcare access challenges. Lastly, there is an urgent need to enhance early detection, diagnosis, and treatment of CMM in low SDI regions in response to the increasing burden of CMM in these areas.

While our study offers valuable insights into the global burden of CMM among the elderly, it has some limitations.[28–30] First, it did not account for the impact of the COVID-19 pandemic from 2020 to 2022 on access to healthcare resources, diagnostic delays, and treatment impediments. This omission may have resulted in an underestimation of morbidity and mortality data. Second, country-level data may obscure regional disparities, such as the unequal disease burdens between urban and rural areas or across different geographic regions in countries with large landmasses. Additionally, the accuracy of data frameworks that rely on GBD studies is constrained by the completeness of national cancer registry systems. Consequently, the true burden of CMM may be significantly underestimated in low- and middle-income countries due to issues such as underreporting, underdiagnosis of pathology, and delayed data reporting.

Although the GBD modeling framework uses sophisticated Bayesian meta-regression (DisMod-MR 2.1) to address data gaps and improve comparability, estimates for data-sparse regions are associated with wider uncertainty intervals and may still reflect reporting trends alongside true epidemiological changes. Therefore, the dramatic increasing trends we observed in certain low and low-middle SDI regions might be partly driven by improvements in healthcare access and diagnosis over the 31-year study period. This limitation necessitates a cautious interpretation of both the absolute burden and the temporal trends in these areas, suggesting that the reported figures might represent a conservative estimate. Nonetheless, the GBD provides the most systematic platform for global comparison, and our findings reliably highlight critical geographic disparities and signal regions where public health focus on CMM in the elderly should be prioritized.

Our study calls for a dynamic and targeted re-evaluation of global CMM control strategies. To translate these findings into action, we propose the following specific interventions, aligned with current public health and clinical best practices:

In low-latitude regions and low SDI regions with rapidly increasing burden, health authorities should prioritize primary prevention by adapting and implementing evidence-based, low-cost UV protection campaigns. These can be modeled on the core principles of the Australian "Slip-Slop-Slap-Seek-Slide" campaign and the World Health Organization's INTERSUN Programme, which emphasize the use of clothing, sunscreen, shade, and avoiding peak sun hours.[27]

To address the significant gender disparity, targeted secondary prevention strategies for elderly men are crucial. This could include integrating opportunistic skin examinations into primary care visits for other common conditions (eg, hypertension, diabetes), leveraging community events like "Men's Health Week," and promoting the use of visual aids and mobile technologies for structured skin self-examination, as recommended by various dermatology associations.

For healthcare systems, there is an urgent need to develop capacity for the management of elderly CMM patients. This involves creating geriatric-adapted clinical pathways, in line with the guidelines from the International Society of Geriatric Oncology (SIOG). Implementing Geriatric Assessment (GA) before major treatment decisions can identify vulnerabilities related to comorbidities, functional status, and cognitive function, thereby personalizing therapy to optimize both survival and quality of life.[31]

By benchmarking interventions against these established frameworks, we provide a concrete and feasible roadmap for mitigating the growing burden of CMM in the aging global population.

While this study provides a comprehensive epidemiological overview, its ecological and retrospective nature inherently limits causal inference. To address these limitations and build upon our findings, we propose a concrete roadmap for future research: Future studies should employ spatial regression models and panel data analysis to quantitatively link time-series data on ambient UVR, temperature, and other environmental factors with CMM burden across different regions, while rigorously controlling for sociodemographic confounders. This would provide stronger evidence for the environmental drivers suggested by our maps and trends.

Our population-level findings, particularly the striking gender and age disparities, necessitate validation at the individual level. There is an urgent need for prospective cohort studies specifically designed in the rapidly evolving regions we identified (eg, the Middle East and Latin America). These cohorts should collect detailed data on individual sun exposure history, genetic ancestry, skin phenotype, and comorbidities to disentangle the complex web of risk factors and better inform targeted prevention.

Ultimately, our results should seed interventional research. Randomized Controlled Trials (RCTs) are needed to test the efficacy and cost-effectiveness of proposed actions, such as male-targeted community screening programs using tele dermatology. Furthermore, implementation science studies are crucial to evaluate the feasibility and impact of integrating

geriatric assessment into standard melanoma care pathways in diverse healthcare settings, with the goal of improving treatment decisions and survival for elderly patients.

Conclusion

This study analyzes the global burden of CMM in individuals aged 60 years and elderly from 1990 to 2021, revealing significant regional disparities. Populations residing at lower latitudes exhibit a higher burden of CMM. The study advocates for enhanced protective measures in low SDI regions with elevated UV exposure, encourages targeted screening for men, and emphasizes the need for dynamic optimization of global prevention and control strategies that consider regional differences.

Data Sharing Statement

Data resources from the GBD study 2021 could be accessed online through the Global Health Data Exchange (GHDx) query tool (http://ghdx.healthdata.org/gbd-results-tool).

Ethics Statements

According to Article 32 of the Ethical Review Measures for Life Science and Medical Research Involving Human Beings of the People's Republic of China, the data used in this study will not cause any form of harm to human beings, nor will it touch sensitive personal privacy or trade secrets, so the ethical review can be exempted. In addition, the database used in this study was publicly available and legally available.

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Disclosure

The authors declare no competing interests.

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