Hindawi
European Journal of Cancer Care
Volume 2023, Article ID 5484597, 8 pages
https://doi.org/10.1155/2023/5484597

Research Article

The Global, Regional, National Burden of Cutaneous Squamous Cell Carcinoma (1990–2019) and Predictions to 2035

Aiyuan Guo,[1] **Xiajing Liu**,[2] **Heqing Li**,[3] **Wenwei Cheng**,[4,5] **and Yexun Song**[3]

[1]*Department of Dermatology, The Third Xiangya Hospital of Central South University, Changsha 410013, Hunan, China*
[2]*Graduate School of Guilin Medical University, Guilin 541004, Guangxi, China*
[3]*Department of Otolaryngology-Head Neck Surgery, The Third Xiangya Hospital of Central South University, Changsha 410013, Hunan, China*
[4]*The Third Xiangya Hospital of Central South University, Changsha 410013, Hunan, China*
[5]*Xiangya School of Public Health, Central South University, Changsha 410000, Hunan, China*

Correspondence should be addressed to Wenwei Cheng; wennweichen@163.com and Yexun Song; yexunsongent@csu.edu.cn

Received 1 October 2022; Revised 22 January 2023; Accepted 4 February 2023; Published 21 April 2023

Academic Editor: Natasja Raijmakers

Objective. The aim of the study is to provide the burden of cutaneous squamous cell carcinoma (cSCC) in 21 regions, 204 countries, and territories from 1990 to 2019 by age, sex, and sociodemographic index (SDI) and to predict the global burden of cSCC to 2035. *Methods*. We use estimates from 2019 Global Burden of Disease (GBD) study to conduct the analysis and prediction. The burden of cSCC was estimated for 21 regions, 204 countries, and territories from 1990 to 2019, through a systematic analysis of incidence, death, and disability adjusted life years (DALYs) modelled data using the methods reported in the GBD 2019 study. We predicted the age-standardized incidence rates to 2035 at the global, regional, and national level. Results. There were 2,402,221 global incidence cases and 356,054 deaths in 2019. The age-standardized incidence rate was 30.3 and the age-standardized death rate was 0.7. cSCC, which caused 1.2 million DALYs with an ASR of 14.6 in 2019. Between 1990 and 2019, the age-standardized incidence rate increased by 36.1%, death rate increased by 6.1%, and DALY rate increased by 1.5% globally. At the regional level, the highest age-standardized incidence rate was found in high-income North America, the highest death and DALY rates were shown in Australasia. At the national level, Canada had the highest age-standardized incidence and DALY rates in 2019, and the highest death rate was shown in Tonga. A total of 11 GBD regions and 114 countries were predicted to increase in age-standardized incidence rates between 2019 and 2035, respectively. *Conclusions*. The cSCC is a major global public health challenge and the burden was often underestimated. The burden is increasing in most countries, especially in countries such as Canada, China, and regions such as Caribbean.

1. Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer. It accounts for 20% of skin cancers in the United States [1]. A survey showed an increased incidence rate from 61.8 (1976–1984) to 162.5 per 100,000 person-years (2000–2010) in Olmsted County, Minnesota [2]. The age-standardized incidence rates of cSCC in Europe ranges from 9 to 96 among male inhabitants and 5 to 68 among female inhabitants (2002–2007) [3]. The data from the Netherlands showed that the age-standardized rates increase substantially from 2002 to 2017, especially among female patients [4]. Due to the growing incidence rates of cSCC, it is significant to make an analysis of the burden of cSCC globally so that we can give convincing evidence for those policy makers to prevent the occurrence of cSCC in the future.

Previous studies have presented the burden and trends of cSCC mainly focused on the national level, which could not reflect the global and regional burden so as to pay more attention to the regions, which may be ignored before. In addition, these studies only reported one metric, not the systematic analysis of disease burden and trends [5, 6]. Although we found a few research studies that predicted the

temporal trends of the incidences of cSCC, the trends in the epidemiology and burden of cSCC are changing, reinvestigating, and predicting the geographical differences and trend changes, which is essential. The aim of this study is to analyze and predict the burden of cSCC at global, regional, and national level from 1990 to 2035, so as to provide essential epidemiological data for cancer prevention.

2. Materials and Methods

2.1. Study Data. In this study, data on the disease burden of cSCC were obtained through an online query tool from the website of the Institute for Health Metrics and Evaluation (IHME) (https://ghdx.healthdata.org/). The general methodology of GBD 2019 developed by IHME has been explained in the previous publications [7–11]. This study followed the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) reporting guideline for cross-section studies [12].

2.2. Statistical Analysis. We used counts and age-standardized rates (ASRs) per 100,000 people from 1990 to 2035, with 95% uncertainty intervals (UIs). Incidence, deaths, DALYs, prevalence, years of life lost (YLL), and years lived with disability (YLD) were used to estimate the burden of cSCC and stratified by age, sex, year, location, and SDI category from the GBD online platform. We also calculated percentage change of counts and ASRs between 1990 and 2019. Detailed information about the estimation process is described in Supplementary Materials.

The autoregressive integrated moving average (ARIMA) model is one of the most commonly used parameter models of time-series models by forecasting the future trends based on historical values. The complete form of the nonseasonal ARIMA model is defined as ARIMA (p, d, and q), where AR is autoregression and p is the order for the autoregressive expression, MA is moving average and q is the order for the moving average expression, and $I(d)$ represents the differences required by the time-series in order to be stationary [13]. We use the ARIMA model time-series method to forecast the age-standardized rate of incidence for the upcoming sixteen years until the end of 2035 in this research study.

The R statistical software program (version 4.0.3) or SPSS 25.0 (IBM Corporation, New York, USA) were used in this research. The p value <0.05 was considered significant statistically.

3. Results

3.1. Observed Trends

3.1.1. Global Level. In 2019, cSCC accounted for 2,402,221 (2,122,698 to 2,712,803) incidence cases and 56,054 (50,415 to 59,792) death cases globally. The age-standardized incidence rate of cSCC was 30.3 (26.9 to 34.1) and the death rate was 0.7 (0.7 to 0.8). Around 1.2 million (1,084,052 to 1,262,186) DALYs were due to cSCC, with ASRs of 14.6 (13.4 to 15.6) (Table S1, Figures S2, S3, and S9). The incidence, death, and DALYs for cSCC for both sexes by the Global Disease Burden region in 1990 are shown in Table S4.

The global age-standardized incidence rate increased by 36.1% (19.5% to 54.1%), mortality rate increased by 6.1% (−1.2% to 13.7%), and DALY rate increased by 1.5% (−5.6% to 8.8%) from 1990 to 2019 (Table S1, Figures S11–S13).

3.1.2. Regional Level. High-income North America (324.2, 85.9 to 368.5), Australasia (249.7, 210, to 294.7), and Southern Latin America (9.9, 8.6 to 11.2) had the highest age-standardized incidence rates, while these rates were the lowest in South Asia (0.4, 0.3 to 0.4), Western Sub-Saharan Africa (0.5, 0.4 to 0.6), and Oceania (0.7, 0.6 to 0.8). Australasia (1.7, 1.5 to 1.8), Caribbean (1.4, 1.2 to 1.6), and Central Latin America (1.2, 1.0 to 1.4) had the highest age-standardized death rates, while these rates were lowest in South Asia (0.4, 0.3 to 0.4), high-income Asia Pacific (0.4, 0.3 to 0.4), and Western Sub-Saharan Africa (0.4, 0.3 to 0.4). Australasia (38.7, 34.1 to 44.2), high-income North America (30.9, 25.1 to 38.8), and Caribbean (25.7, 21.6 to 29.7) had the highest age-standardized DALY rates in 2019, while high-income Asia Pacific (6, 5.4 to 6.4), South Asia (6.5, 5 to 7.8), and Western Sub-Saharan Africa (7.7, 5.9 to 9.3) had the lowest DALY rates (Table S1).

3.1.3. National Level. The highest age-standardized incidence rates in 2019 were shown in Canada (828.1, 662.3 to 1019.4), Greenland (576.2, 461.2 to 702.1), and the United States of America (262.2, 235.1 to 293.4). In 2019, the age-standardized death rates were the highest in Tonga (2.5, 1.9 to 3.1), Cuba (2.0, 1.6 to 2.4), and New Zealand (1.9, 1.3 to 2.1). On the contrast, the lowest death rates were found in Egypt (0.2, 0.2 to 0.3), Sao Tome and Principe (0.3, 0.2 to 0.3) and Singapore (0.3, 0.2 to 0.3) (Figure 1(b)) (Table S6). The highest age-standardized DALY rates were found in Canada (65.7, 44.9 to 94.0), Greenland (50.0, 34.9 to 69.9) and Tonga (43.0, 33.7 to 54.5). Conversely, Egypt (4.5, 3.2 to 6.1), Singapore (5.0, 4.4 to 5.7), and Syrian Arab Republic (5.3, 4.0 to 6.9) had the lowest DALY rates (Figure S10) (Table S6).

Between 1990 and 2019, the percentage change in age-standardized incidence rates differed, with the Canada (311.5%, 242.6% to 389.6%), China (163.7%, 145.2% to 187.1%), and Portugal (126.3%, 87.7% to 166.3%) showing the largest increases. By contrast, Thailand (−34.0%, −39.5% to −28.6%), Sri Lanka (−32.3%, −35.5% to −28.6%), and Republic of Korea (−27.0%, −34.5% to −18.9%) showed the largest decreases. The percentage change in age-standardized death rates also differed. The largest increases were observed in Bosnia and Herzegovina (513.4%, 364.8% to 675.9%), Saint Kitts and Nevis (471.2%, 67.1% to 618.5%), and Antigua and Barbuda (408.2%, 72.0% to 530.2%). By contrast, the largest decreases were found in Republic of Korea (−54.8%, −61.0% to −47.3%), Taiwan (−48.7%, −59.7% to −29.0%), and Thailand (−47.0%, −62.3% to −27.4%). In terms of age-standardized DALY rates, the largest increases were observed in Saint Kitts and Nevis (455.5%, 52.6% to 623.7%), Bosnia and Herzegovina (363.5%, 247.7% to 484.6%), and Antigua and Barbuda (312.5%, 43.7% to

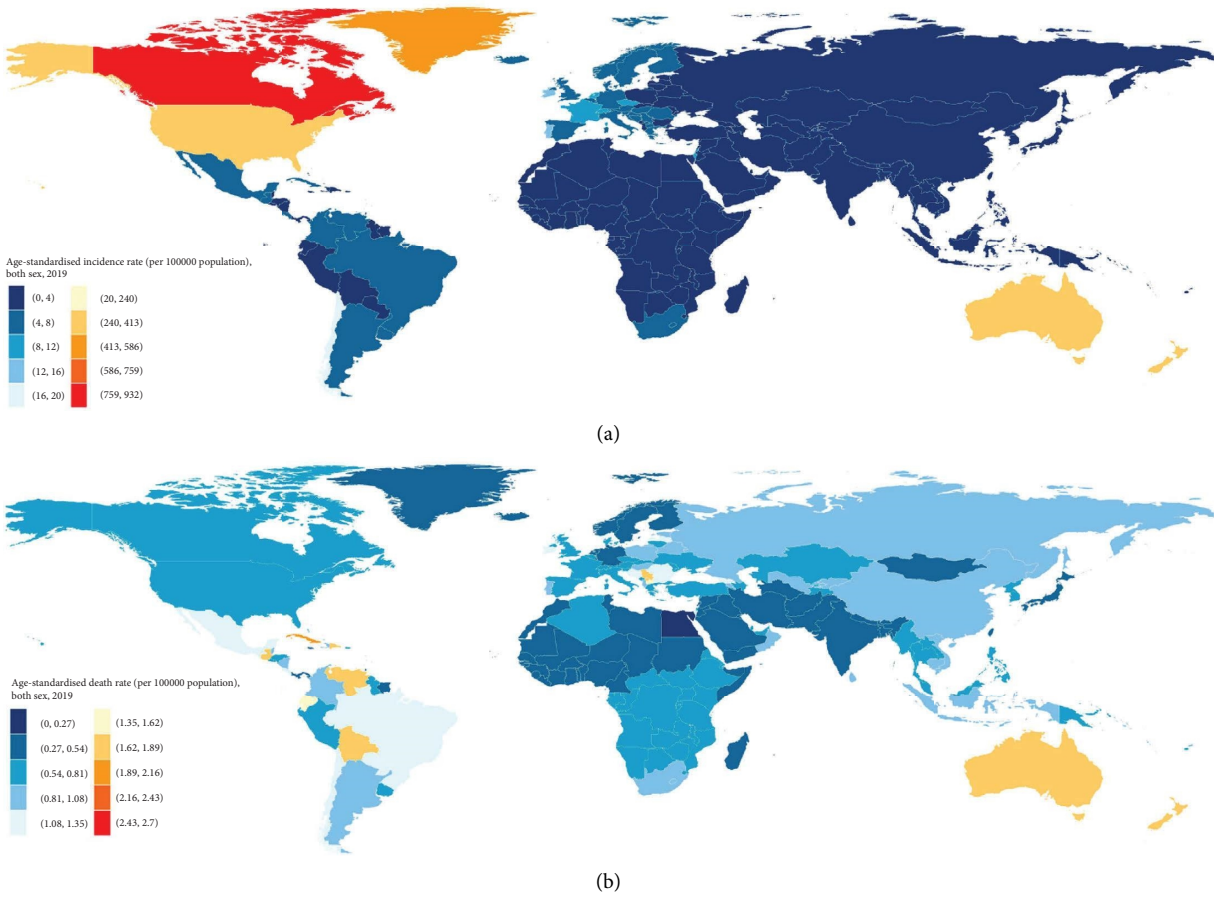

Figure 1: Age-standardized incidence (a) and death (b) rates of cSCC per 100000 population for both sex, 2019.

416.3%). The largest decreases were found in Republic of Korea (−61.9%, −66.0% to −57.2%), Taiwan (Province of China) (−50.2%, −62.0% to −28.6%), and Poland (−49.3%, −56.7% to −37.1%) (Table S6).

Additionally, the age-standardized prevalence rate of cSCC was the highest in Czechia (9.7, 8.3 to 1.3), with an increased trend from 1990 to 2019 (59.5%, 40.5% to 79.4%); the age-standardized YLL rate of cSCC was the highest in Panama (9.9, 7.5 to 12.7), with an increased trend from 1990 to 2019 (6.9%, −21.0% to 39.9%); the age-standardized YLD rate of cSCC was highest in Canada (54.4, 33.3 to 82.9), with an increased trend from 1990 to 2019 (239.7%, 173.6% to 309.1%). More details could be found in supplementary Table S7.

3.1.4. Age and Sex Patterns. In 2019, the total counts of incidence, deaths, and DALYs followed a normal distribution, peaking at 70–74 years for incidence cases, 65–69 years for DALYs, 80–84 years for male death cases, and 85–89 years for female death cases (Figure 2).

In 2019 for both sexes, the age-standardized rates of incidence, death, and DALY increased in a linear manner as age increased, peaking at 95 plus years. All of the global age-standardized rates were higher in males than in females across all the age groups (Figure 2).

Most of the incidence, death, and DALY numbers were higher among males than females in 2019, except for deaths in Eastern Europe, and incidence numbers in Australasia, Eastern Europe, high-income Asia Pacific, Southern Latin America, and Tropical Latin America (Table S2). The age-standardized incidence, death, DALY rates in 2019 for males and females in 21 GBD regions were shown in Figure S18.

Between 1990 and 2019, the percentage change in the age-standardized incidence, death, and DALY rates differed in all the GBD regions among males and females (Figure S25).

3.1.5. Burden of cSCC by the Sociodemographic Index (SDI). At the regional level, the trends in the age-standardized DALY rates across SDI from 1990 to 2019 were shown in Figure 3(a). The expected pattern was nonlinear and peaking at an SDI value of approximately 0.75, before decreasing with increasing SDI values. Among the 21 GBD regions, the trends in the age-standardized DALY rates differed with increasing SDI values (Figure 3(a)).

At the national level, the expected patterns of age-standardized DALY rates were nonlinear in nature. Many countries, such as Canada, Greenland, and Tonga had higher age-standardized DALY rates than the expected levels;

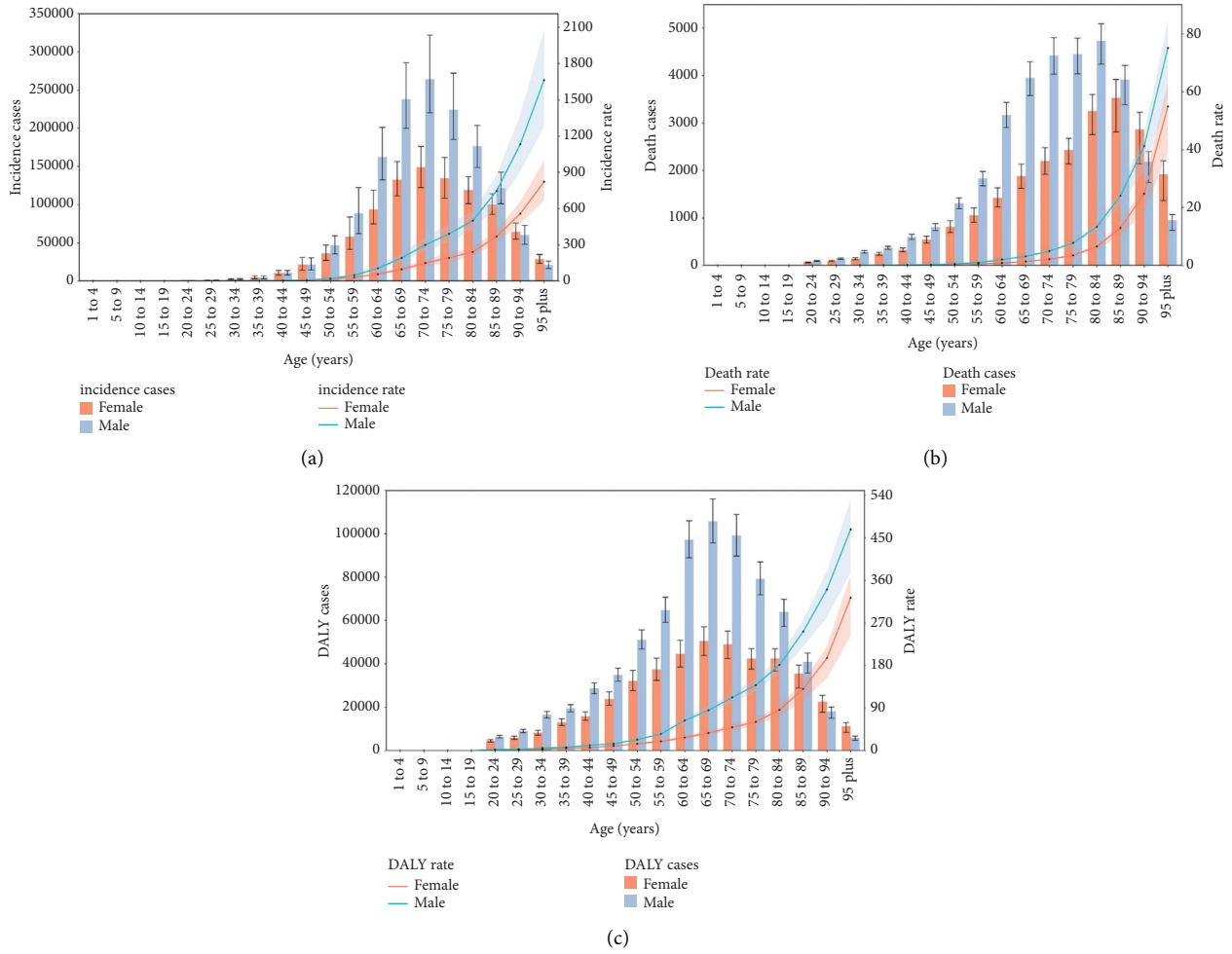

Figure 2: Global counts and age-standardised incidence (a) death (b) and DALY (c) rates of cSCC per 100000 population by age and sex, 2019. Error bars indicate the 95% UI. Shading indicates the upper and lower limits of the 95% UI.

whereas others, such as Egypt, Nepal, and Japan had lower than the expected levels (Figure 3(b)).

3.2. Predicted Incidence Trends

3.2.1. Global Level. The predicted age-standardized incidence rate is 32.2 (16 to 48.4) in 2035, which increase by 6.4% from 2019 to 2035 (Figure 4). The total counts of incidences are 3637626 (2802867 to 4472386) in 2035, which increase by 51.4% from 2019 to 2035 (Table S8.)

3.2.2. Regional Level. Figure 4 and Table S8 show the trends in cSCC cancer incidence between 2019 and 2035 for the 21 GBD regions. From 2019 to 2035, the age-standardized incidence rates in 11 regions are projected to increase, especially in East Asia (186.1% increase), Southern Latin America (173.2% increase), high-income Asia Pacific (91.6% increase). From 2019 to 2035, the age-standardized incidence rates in 10 regions are projected to decrease, especially in North Africa and the Middle East (−137.0% decrease), Central Latin America (−97.0% decrease), and Oceania (−42.1% decrease).

3.2.3. National Level. Table S9 presents the projected trends of incidence from 2019 to 2035. From 2019 to 2035, the age-standardized incidence rates in 89 countries are projected to decrease, especially in Turkey (−421.5% decrease), Lebanon (−354.1% decrease), United Kingdom (−325.3% decrease); the age-standardized incidence rates in 114 countries are projected to increase, especially in China (190.5% increase), Austria (187.8% increase), and Chile (169.9% increase). The temporal trends of ASRs of cSCC between 1990 and 2019 and their projections through 2035 in 204 countries are shown in the Supplementary Figure S33, with the top 10 highest ASRs shown in Figure 5.

4. Discussion

In this study, we presented counts and age-standardized rates of incidence, death, and DALYs for cSCC in global, 21 regions, and 204 countries from 1990 to 2019. It showed that the burden of cSCC in 2019 is almost as high as the burden of melanoma in 2015, which is the deadliest skin cancer [14]. And the global incidence cases and age-standardized incidence rates of cSCC were projected to increase continuously from 2019 to 2035. Correspondingly, a study

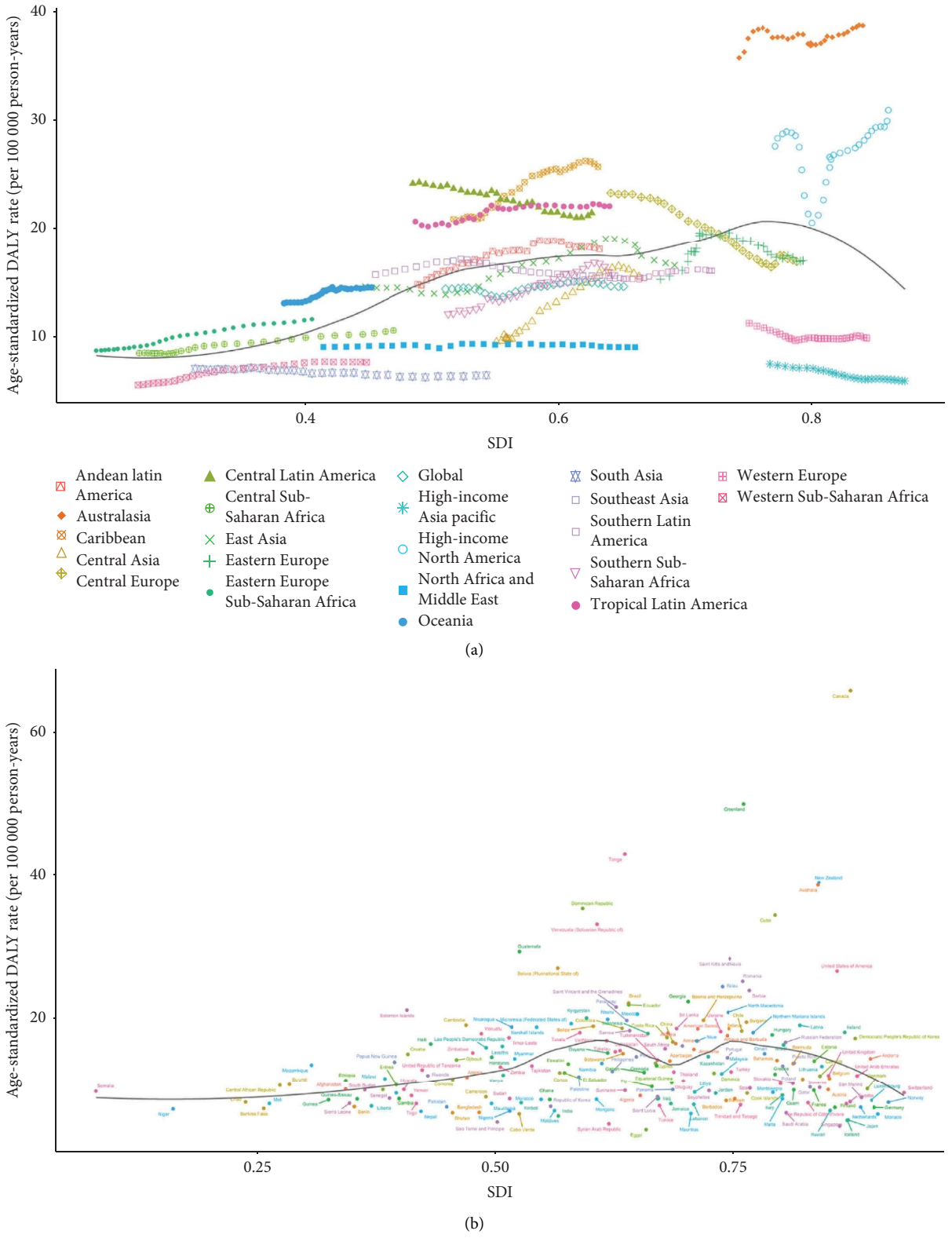

FIGURE 3: Age-standardized DALY rates for 21 GBD regions (a) from 1990 to 2019 and for 204 countries (b) in 2019 by SDI. The black line represents the expected age-standardized DALY rates.

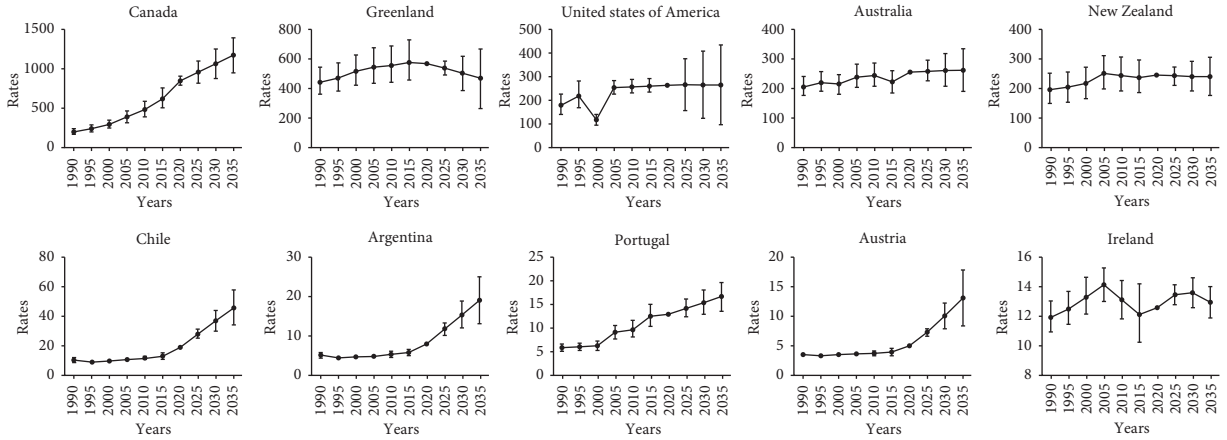

Figure 4: The global and regional trends of age-standardized incidence rates of cSCC from 1990 to 2035.

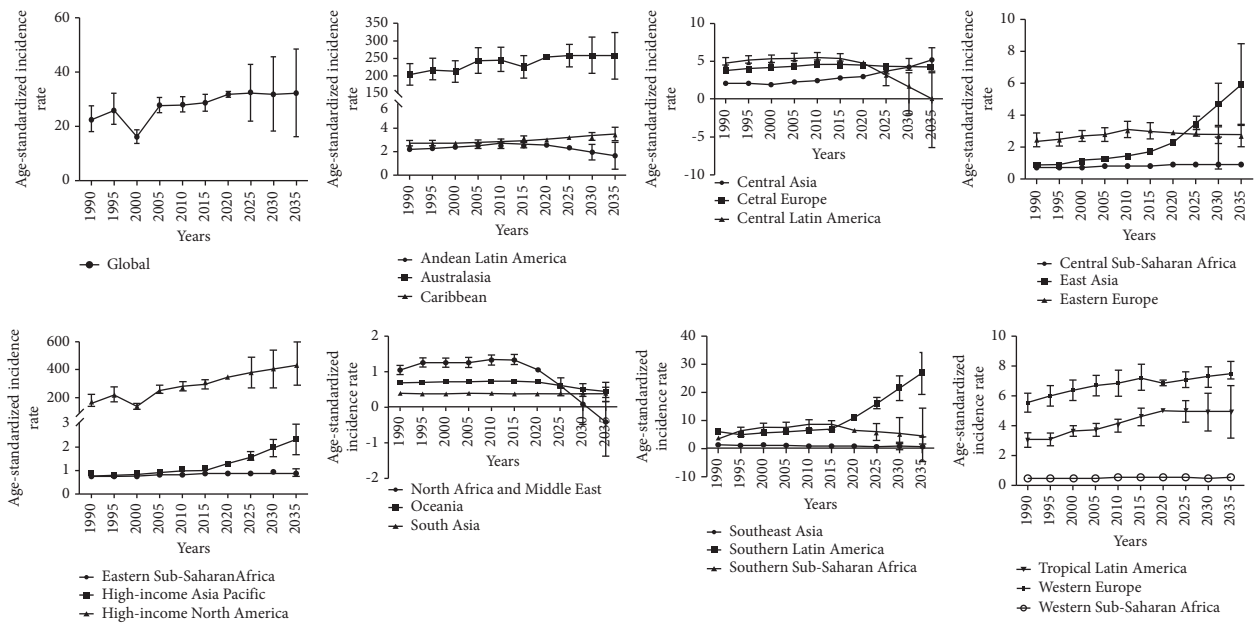

Figure 5: The national trends of top 10 highest age-standardized incidence rates from 1990 to 2019 and their projections through 2035.

conducted by Burton et al. showed that the incidence of nonmelanoma skin cancer, including cSCC is expected to rise until the year 2040 [15]. These data serve to highlight the significant, yet underestimated, global burden of cSCC.

As shown here and in the previous studies, the burden of cSCC was higher in men than in women [16]. It has been well documented that men are more likely to have outdoor occupations and leisure activities, and to use less sunscreen than women [17]. Hence prevention measures should pay extra attention to men. The ASRs of incidence, death, and DALY increased with age, peaking at the oldest age group for both women and men in 2019. It is likely to be a result of prolonged, lifelong exposure to risk factors [18].

We reveal that the highest ASRs of incidence and DALY of cSCC were in Australasia and North America, and Australasia also had the highest death rate in 2019. Reasons for the high burden of cSCC in these regions were attributable to susceptible fair-skinned population, high ambient UV radiation levels, and a cultural emphasis on tanning [19]. It is interesting to notice that, although Caribbean had low age-standardized incidence rate in 2019, it had high age-standardized death rates and DALYs. One of the explanations may be that the area is largely non-white. In non-white individuals, cSCC behaves more aggressively, resulting in scars, burn sites, or chronic inflammation (Marjolin ulcer) in sun-protected skin regions [20], which was found to elevate the risk of short-term death [21]. Other explanations need further explorations and research studies.

The highest incidence rate reported in the previous studies was in Australia [22]. However, it has a stable or declining incidence rate in recent years. The age-standardized incidence rate of Australia was 250.4 in 2019, and the percentage change increased slightly from 1990 to 2019. Different from the previous data, our study showed that, Canada had the highest level of age-standardized incidence rates and DALYs in 2019, together

with the highest percentage change in the age-standardized incidence rates from 1990–2019. A review analyzed the trends in cSCC in Canada from 1960 to 2010 observed that the incidence increased in four Canadian cities and Manitoba had the highest annual percentage change for males and females at 3.27% and 3.73% (1960–2000), respectively [23]. This study found larger changes in the incidence rates than the review that is cited. Therefore, the burden in Canada was underestimated, and more attention should be paid to cSCC in Canada in the future. The high burden of cSCC in Australia and Canada may be the result of fair skin, UV exposure, cultural habits of outdoor recreation, and population aging [22, 24]. However, Australia has undertaken aggressive and comprehensive skin cancer awareness campaigns since 1980 to reduce the burden of skin cancer [25]. Australia has enacted strict countrywide bans on the commercial use of indoor tanning for cosmetic purposes for all individuals [24]. In contrast, Canada has lagged behind Australia in skin cancer prevention efforts and the implementation of protective behaviors. The implementing bans on indoor tanning are at a start status, and more efforts should be made to enact more policies and ensure compliance with these policies effectively.

There were a few studies carried out about the burden for cSCC in China. China had the second highest percentage change in age-standardized incidence rates from 1990 to 2019 following Canada, and China was predicted to have the highest age-standardized incidence rates from 2019 to 2035. The dramatic upward trend for incidence rates may be explained by the population growth, aging, improved public awareness regarding suspicious pigmented lesions, and the earlier detection. Especially, the application of skin reflection confocal microscope can detect the disease early and noninvasively [26]. Therefore, a series of measures should be taken to prevent the occurrence of the disease and reduce the incidence of cSCC.

To the best of our knowledge, the present study examined the correlations of DALYs with the developing status of region and countries for the first time. It suggested that the correlation between DALYs and SDI should not be assumed to be simplistic and linear; GBD 2019 showed a complex and nonlinear association. Many countries with high SDI represent much higher burden than the expected burden level, like Canada, New Zealand, Australia, and the United States of America. In fact, the burden of cSCC is not only related to SDI but also closely related to sun exposure, skin color, age, gender, and lifestyle.

There were limitations in our research study. First, the quality and the quantity of data from the GBD highly determined the accuracy of our study. The center for disease control and prevention in some underdeveloped areas was not available to provide accurate and timely data. Second, the influence of more detailed factors such as race, pathological type, and location of disease were not taken into account in the GBD datasets. We could not estimate the attributable risk factors of cSCC burden. These risk factors may include UV exposure, older age, men, fair skin and immunosuppression, race, and pathological type.

5. Conclusions

The cSCC is a major global public health challenge. However, the burden varied geographically and was underestimated in the previous studies. This is the first study to systematically and comprehensively estimate and predict the burden of cSCC. Our findings can be used to guide the prevention measures.

Abbreviations

DALYs: Disability-adjusted life-years
SDI: Sociodemographic index
GBD: Global burden of disease, injuries, and risk factors study
YLLs: Years of life lost
YLDs: Years lived with disability
IHME: Institute for Health Metrics and Evaluation
GATHER: Guidelines for accurate and transparent health estimates reporting
ASRs: Age-standardized rates
UIs: Uncertainty intervals
cSCC: Cutaneous squamous cell carcinoma.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request (https://ghdx.healthdata.org/gbd-results-tool).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yexun Song and Aiyuan Guo designed the research, Xiajing Liu analyzed the raw data, Wenwei Cheng and Heqing Li conducted the statistical analyses, and Yexun Song wrote the main manuscript. All authors reviewed the drafted manuscript for critical content and approved the final version.

Acknowledgments

The authors would like to thank all the members of the Institute for Health Metrics and Evaluation (IHME), and Bill & Melinda Gates Foundation who support the related GBD 2019 studies. This work was supported by the grants from the National Science Foundation of China (81702706), National Science Foundation of Hunan Province (2020JJ5866), and the Wisdom Accumulation and Talent Cultivation Project of the Third Xiangya Hospital of Central South University (YX202210).

Supplementary Materials

We also analyzed the prevalence, YLL and YLD counts and rates of cSCC cancer in global, regional and national level in 2019 (Supplemental Methods, Figure S1, S4–8, S14–S16, S19–24, S26–32 and Table S3, S5, S7). Moreover, the

temporal trends of the age-standardized incidence rates between 1990 and 2019 and their projections through 2035 in 204 countries were shown in the supplementary figure. Table S10 and Figure S17 showed the SDI quintile in 2019. GBD 2019 sequelae, health states, health state lay descriptions, and disability weights for cSCC were shown in Table S11. For more details, see Supplemental Material. (*Supplementary Materials*)

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