Am J Cancer Res 2025;15(3):1002-1019
www.ajcr.us /ISSN:2156-6976/ajcr0163567

Original Article

Global, regional, and national burden of premenopausal and postmenopausal malignant melanoma from 1990 to 2021: a comprehensive cross-sectional analysis

Xingchen Liu[1,3*], Chengling Liu[2*], Jiayu Li[3,4*], Yanfang Liu[1], Liqiang Hao[4], Meng Guo[3], Jianming Zheng[1]

[1]Department of Pathology, The First Affiliated Hospital of Naval Medical University, Shanghai, China; [2]Center of Burns and Plastic Surgery and Dermatology, The 924th Hospital of Joint Logistics Support Force of The PLA, Guilin, Guangxi, China; [3]National Key Laboratory of Immunity and Inflammation and Institute of Immunology, Naval Medical University, Shanghai, China; [4]Department of Colorectal Surgery, The First Affiliated Hospital of Naval Medical University, Shanghai, China. [*]Equal contributors.

Received January 25, 2025; Accepted February 17, 2025; Epub March 15, 2025; Published March 30, 2025

Abstract: Malignant melanoma is a highly fatal disease closely associated with sex hormones. This study aimed to evaluate the global burden and trends of malignant melanoma based on menopausal status. Data on the prevalence, disability-adjusted life years (DALYs), and mortality of malignant melanoma were obtained from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021. Age 55 was used as a threshold for menopausal status to assess global, regional, and national trends in disease burden among women. In 2021, the age-standardized prevalence rate (ASPR) of malignant melanoma was higher in women than men under 55 years but lower in women over 55 years. From 1990 to 2021, the ASPR for premenopausal women increased from 14.23 [95% uncertainty interval (UI) (13.79-14.60)] to 16.53 [95% UI (15.09-17.78)], while the age-standardized DALYs rate (ASDR) decreased from 14.04 [95% UI (12.20-15.61)] to 11.83 [95% UI (9.20-14.35)], and the age-standardized mortality rate (ASMR) decreased from 0.27 [95% UI (0.24-0.30)] to 0.23 [95% UI (0.18-0.28)]. For postmenopausal women, the ASPR increased from 55.01 [95% UI (51.71-57.23)] to 81.43 [95% UI (74.33-87.03)], while the ASDR decreased from 63.88 [95% UI (58.39-69.64)] to 56.11 [95% UI (48.79-63.66)], and the ASMR decreased from 2.96 [95% UI (2.69-3.19)] to 2.73 [95% UI (2.36-3.07)]. The disease burden was highest in high socio-demographic index (SDI) regions but has recently decreased, whereas a gradual increase was observed in high-middle SDI regions. At the national level, New Zealand had the highest ASPR for both premenopausal and postmenopausal women, with values of 245.63 [95% UI (209.56, 279.91)] and 909.37 [95% UI (754.63, 1037.39)], respectively. Regional variations in population-level determinants of disease burden were identified. The risk and prognosis of malignant melanoma in women may differ by menopausal status due to the interplay of sex hormones and the immune system. Further research is needed to develop tailored screening and treatment strategies for women across diverse SDI regions and menopausal statuses.

Keywords: Malignant melanoma, global burden of disease, menopausal status, socio-demographic index

Introduction

Malignant melanoma is the most lethal type of skin tumor and originates from melanocytes. Excessive exposure to ultraviolet (UV) radiation is widely accepted as a major causative factor of malignant melanoma. A registry-based study indicates that the average age at diagnosis of malignant melanoma is 3-8 years younger in women than in men [1]. The high incidence of melanoma in young women is not solely attributable to UV exposure from sunbathing; gender itself is an independent risk factor in these patients. Contrarily, female gender appears to have a protective effect in older melanoma patients [2, 3]. It is plausible that changes in sex hormone levels could explain this phenomenon and potentially influence susceptibility to malignant melanoma by affecting DNA repair mechanisms and immune function [4-6]. Consequently, comparing the malignant melanoma disease burden and trends in women with dif-

https://doi.org/10.62347/QBVC1497

ferent menopausal status will help further understand the role of sex hormones in the pathogenesis of malignant melanoma and thus provide a basis for personalized prevention and treatment.

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 provides comprehensive data on the prevalence, mortality, and disability-adjusted life years (DALYs) of patients with malignant melanoma of all ages worldwide from 1990 to 2021. Utilizing this data, our study, defining menopause age as 55 years, aimed to (i) compare the burden of malignant melanoma across menopausal status at global, regional, and national levels, (ii) assess trends in malignant melanoma by menopausal status over the past 30 years and predict future trends, and (iii) analyze the driving forces behind these trends.

Methods

Data source and study design

This study used data from the GBD 2021 database (https://vizhub.healthdata.org/gbd-results/) to analyze the global, regional, and national burden of malignant melanoma from 1990 to 2021. GBD studies did not require informed patient consent and adhered to The Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) in population health studies [7]. The GBD 2021 standard population structure is shown in supplementary materials (Table S1). The study focused on female patients with malignant melanoma, stratifying them into two age groups: Premenopausal (10-54 years) and postmenopausal (55 years and older), with 55 years serving as the threshold for menopause [8-10]. The data encompassed 204 countries and regions and covered malignant melanoma prevalence, mortality, and DALYs. The GBD database compiles global health data through a comprehensive methodology, including systematic literature reviews, hospital records, insurance claims, and national health surveys, ensuring the accuracy and comparability of data across different regions and time periods [11, 12]. This study encompasses five socio-demographic index (SDI) regions and a global region. The SDI categorizes areas into five groups-high (0.810296, 1), high-middle (0.711975, 0.810296), middle (0.618829, 0.711975), low-middle (0.465816, 0.618829), and low (0, 0.465816)-based on indicators such as birth rate, income, and education to support health research and policy development [13].

Statistical analysis

We analyzed the prevalence, mortality, and DALYs of malignant melanoma in pre- and post-menopausal women. DALYs, a combined measure of both years of life lost due to premature mortality and years lived with disability, were calculated for both groups [14]. Previous studies have described techniques for calculating age-standardized rates (ASRs), prevalence, DALYs and mortality [15, 16]. These metrics reflect the global health burden of women with malignant melanoma and were assessed across different regions and SDI groups. In this study, ASRs were calculated using a direct method based on the GBD 2021 world population age standard per 100,000 people to minimize the bias caused by differences in the age structure of the population in different countries or regions. The ASRs included age-standardized DALYs rate (ASDR), age-standardized prevalence rate (ASPR), and age-standardized mortality rate (ASMR) [17].

We identified global inflection points in the ASRs between 1990 and 2021 using Joinpoint analysis to assess estimated annual percentage changes. The average annual percentage change (AAPC) was used to evaluate the overall annual ASRs trends over time, and the annual percentage change (APC) was applied to detect changes within specific segments. The AAPCs represent the annual changes in the APC values, such as increase, decrease, or no change. These trends in the rates under investigation are captured by the AAPCs and their corresponding 95% confidence interval (CI). These statistical methods enabled the evaluation of the significance of ASRs trend shifts and supported the robustness of our findings [18].

To understand the drivers of the increased burden of malignant melanoma in women, we used decomposition analysis, which allowed us to separate the effects of population growth, aging, and epidemiological changes on the increase in prevalence, DALYs, and mortality. This approach followed the method outlined by Gupta et al. and provided a detailed understanding of how these factors have contributed

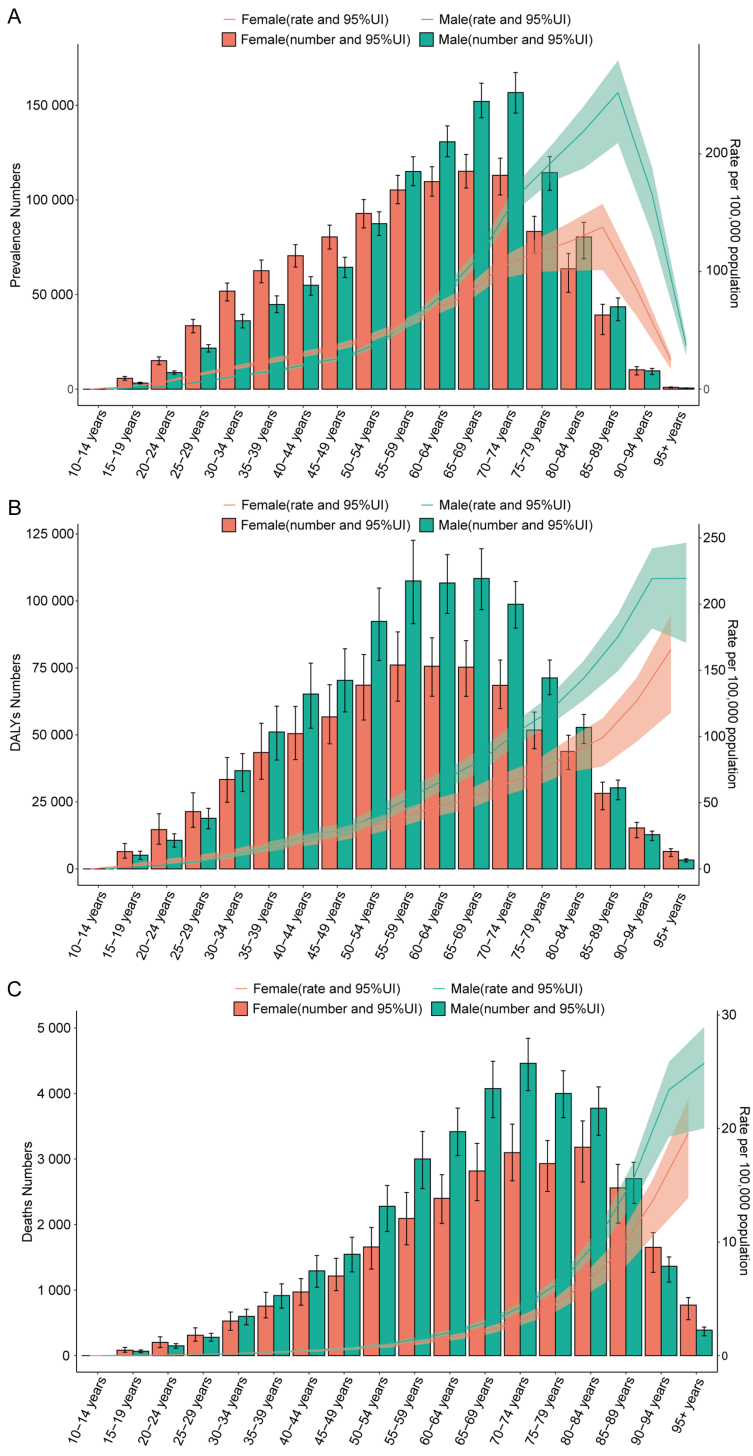

Figure 1. Age-specific patterns by sex for the numbers and age-standardized rates of prevalence, DALYs, and mortality associated with malignant melanoma at the global level in 2021. A. The number of prevalence and the age-standardized prevalence rate of malignant melanoma in different age groups in 2021 by gender. B. The number of DALYs and the age-standardized DALYs rate of malignant melanoma in different age groups in 2021 by gender. C. The number of deaths and the age-standardized mortality rate of malignant melanoma in different age groups in 2021 by gender. Error bars indicated the 95% uncertainty interval (UI) for the numbers. Shaded areas indicated the 95% UI for the rates. DALYs, disability-adjusted life years.

to the rising burden of malignant melanoma in women globally. The detailed analytical methods can be found in previous studies [19].

The 95% uncertainty intervals (UIs) for our estimates were calculated following the standard methodology of the GBD framework. We generated 1,000 draws of the data based on the GBD model, and the lower and upper bounds of the 95% UIs were determined by the 25th and 975th ranked values from these 1,000 simulations [20]. The data visualizations in this study were generated using R software (version 4.2.3) and jD_GBDR (version 2.22; Jingding Medical Technology Co., Ltd.).

Results

Malignant melanoma burden by gender and age

In 2021, among female patients with malignant melanoma, the 65-69 age group accounted for the highest number of cases, while the highest number of cases among male patients was observed in the 70-74 age group. For both genders, the 85-89 age group demonstrated the highest ASPR. Notably, the prevalence and ASPR of malignant melanoma were higher in females than in males up to the 55-59 age group, after which these values became lower in females. This pattern suggests that sex hormone levels may exert protective or risk-enhancing effects in females across different age groups (**Figure 1A**). Based on these findings, we further analyzed the disease burden in female patients according to menopausal status. In 2021, both ASDR and ASMR

increased progressively with age in both males and females, with a steeper rise observed in males (**Figure 1B**, **1C**).

Global, regional, and national burden and trends of malignant melanoma by menopausal status

From 1990 to 2021, the global ASPR for premenopausal malignant melanoma increased from 14.23 [95% uncertainty interval (UI) (13.79-14.60)] to 16.53 [95% UI (15.09-17.78)], whereas for postmenopausal malignant melanoma, the global ASPR increased from 55.01 [95% UI (51.71-57.23)] to 81.43 [95% UI (74.33-87.03)] (**Tables 1** and **2**; **Figure 2A**). From 1990 to 2021, the AAPC for premenopausal malignant melanoma ASPR was 0.08% [95% CI (0.07-0.09)] (**Table 2**). During this period, notable changes in ASPR were observed in 1996, 2010 and 2014. Specifically, from 1990 to 1996, the ASPR exhibited a gradual increase, with an APC of 3.77% [95% CI (3.33-4.21)]. From 1996 to 2010, the upward trend decelerated, with an APC of 1.28% [95% CI (1.11-1.45)]. Subsequently, from 2010 to 2014, the ASPR declined continuously, with an APC of -1.28% [95% CI (-1.98-0.58)], and from 2014 to 2021, the decline became more pronounced, with an APC of -2.56% [95% CI (-2.97-2.15)] (**Figure 3A**). For postmenopausal malignant melanoma, the AAPC of ASPR from 1990 to 2021 was 0.87% [95% CI (0.83-0.09)] (**Table 2**). During this period, the ASPR for postmenopausal malignant melanoma underwent notable changes in 1996, 2009 and 2014. From 1990 to 1996, the ASPR increased significantly, with an APC of 4.18% [95% CI (3.85-4.50)]. From 1996 to 2009, the upward trend slowed slightly, with an APC of 2.29% [95% CI (2.15-2.43)]. From 2009 to 2014, the ASPR remained relatively stable, with an APC of -0.32% [95% CI (-0.84-0.20)], while from 2014 to 2021, the ASPR gradually declined, with an APC of -1.75% [95% CI (-1.99-1.49)] (**Figure 3B**). Although both premenopausal and postmenopausal groups exhibited comparable trends during this period, the magnitude of ASPR changes was more pronounced in the postmenopausal group (**Figure 2A**).

Among the five SDI regions, the ASPR for malignant melanoma was the highest in the high SDI region for pre- and post-menopausal groups, significantly exceeding the world average. However, it has demonstrated a downward trend over the past decade. In 2021, the ASPR in the high SDI region was 82.19 [95% UI (79.42, 85.22)] in the premenopausal group and 250.68 [95% UI (225.58, 265.10)] in the postmenopausal group. The high-middle SDI region had the second-highest ASPR, with a continuous upward trend from 1990 to 2021. The ASPR for the premenopausal group in this region surpassed the world average in 2001, while the postmenopausal group remained below the world average. The other SDI regions exhibited low and relatively stable ASPRs (**Table 2** and **Figure 2D** and **2G**).

In the 21 regions, when the SDI exceeded 0.6, ASPRs in pre- and post-menopausal groups increased significantly with increasing SDI. The highest ASPRs in the premenopausal group were observed in Australasia (ASPR: 206.92, 182.11-233.05), Western Europe (ASPR: 124.01, 117.90-129.69), and High-income North America (ASPR: 95.30, 91.62-99.57) in 2021, while the lowest ASPRs were observed in Oceania (ASPR: 0.11, 0.06-0.17) and Southeast Asia (ASPR: 0.47, 0.29-0.73) (**Table 2** and **Figure 4A**). The highest ASPRs in the postmenopausal group were found in Australasia (ASPR: 639.84, 543.71-727.84), High-income North America (ASPR: 336.11, 305.38-354.89), and Western Europe (ASPR: 312.70, 277.70-335.38) in 2021, while the lowest ASPRs were found in Oceania (ASPR: 0.20, 0.13-0.35) and Southeast Asia (ASPR: 0.82, 0.49-1.30) (**Table 2** and **Figure 4D**). In high SDI regions, the ASPRs exhibited an increasing and then decreasing trend from 1990 to 2021, while in high-middle SDI regions, such as Central Europe and Eastern Europe, the ASPRs demonstrated a continuously increasing trend. Although the High-income Asia Pacific region had a high SDI, the ASPR was lower than those of the high-middle SDI regions (**Figure 4A** and **4D**).

In 2021, the global ASDR for premenopausal malignant melanoma was 11.83 [95% UI (9.20, 14.35)], and the ASMR was 0.23 [95% UI (0.18, 0.28)] (**Table 2** and **Figure 2B**, **2C**). For postmenopausal malignant melanoma, the global ASDR was 56.11 [95% UI (48.79, 63.66)], and the ASMR was 2.73 [95% UI (2.36, 3.07)] in 2021 (**Table 2** and **Figure 2B**, **2C**). From 1990 to 2021, the AAPC for ASDR of premenopausal malignant melanoma was -0.07% [95% CI

Table 1. Estimated number of cases, DALYs, deaths, and age-standardized rates of prevalence (ASPR), DALYs (ASDR), and mortality (ASMR) for premenopausal and postmenopausal malignant melanoma in 1990 at the Global and Regional level

Characteristics	Prevalence				DALYs				Mortality			
	Premenopausal (age <55 years)		Postmenopausal (age ≥55 years)		Premenopausal (age <55 years)		Postmenopausal (age ≥55 years)		Premenopausal (age <55 years)		Postmenopausal (age ≥55 years)	
	Cases	ASPR per 100,000 (95% UI)	Cases	ASPR per 100,000 (95% UI)	DALYs	ASDR per 100,000 (95% UI)	DALYs	ASDR per 100,000 (95% UI)	Deaths	ASMR per 100,000 (95% UI)	Deaths	ASMR per 100,000 (95% UI)
Global	242517.96	14.23 (13.79-14.60)	197994.90	55.01 (51.71-57.23)	239200.26	14.04 (12.20-15.61)	229939.37	63.88 (58.39-69.64)	4650.13	0.27 (0.24-0.30)	10646.71	2.96 (2.69-3.19)
SDI quintiles												
High	189387.72	67.64 (66.07-69.30)	164013.02	155.35 (145.68-161.43)	111584.94	39.85 (38.41-41.57)	125790.14	119.15 (111.81-124.79)	2114.24	0.76 (0.74-0.77)	5929.88	5.62 (5.15-5.89)
High middle	43621.91	12.53 (11.74-13.27)	31065.96	31.93 (30.08-34.12)	64610.43	18.56 (16.56-20.03)	63298.71	65.06 (59.41-70.14)	1295.46	0.37 (0.33-0.40)	2911.23	2.99 (2.74-3.23)
Middle	6174.44	1.09 (0.77-1.31)	1936.47	2.18 (1.64-2.63)	32225.34	5.69 (3.86-7.24)	23703.55	26.64 (19.49-35.96)	639.32	0.11 (0.08-0.14)	1075.61	1.21 (0.89-1.62)
Low middle	1891.63	0.53 (0.33-0.72)	514.61	1.04 (0.74-1.44)	16170.89	4.51 (2.75-6.55)	9355.45	18.90 (13.25-28.02)	316.65	0.09 (0.05-0.13)	407.31	0.82 (0.57-1.18)
Low	1228.75	0.82 (0.44-1.19)	307.98	1.70 (0.99-2.40)	14238.85	9.95 (5.02-13.69)	7417.74	40.87 (24.30-58.86)	277.02	0.19 (0.10-0.27)	305.02	1.68 (1.01-2.42)
GBD Regions												
Andean Latin America	148.12	1.20 (0.88-1.70)	66.50	3.86 (2.76-5.16)	1090.84	8.83 (6.21-13.26)	1145.51	66.52 (46.91-91.04)	22.13	0.18 (0.13-0.27)	57.40	3.33 (2.34-4.46)
Australasia	13242.98	201.33 (181.53-223.77)	10876.88	510.08 (455.90-573.60)	7725.90	117.45 (108.41-127.26)	9939.03	466.10 (415.45-524.97)	144.02	2.19 (2.02-2.35)	475.45	22.30 (19.72-25.32)
Caribbean	269.60	2.29 (2.07-2.56)	128.92	5.80 (5.18-6.48)	786.31	6.68 (5.19-9.28)	650.93	29.26 (25.04-36.38)	15.44	0.13 (0.10-0.18)	31.81	1.43 (1.25-1.72)
Central Asia	668.11	3.05 (2.70-3.41)	505.84	10.63 (9.39-11.96)	2115.87	9.67 (8.50-10.97)	2698.41	56.72 (50.13-63.65)	42.35	0.19 (0.17-0.22)	134.18	2.82 (2.48-3.20)
Central Europe	8455.34	21.43 (19.83-24.02)	5723.94	38.00 (34.92-42.85)	17409.73	44.13 (41.10-49.69)	17698.39	117.48 (109.37-128.79)	354.94	0.90 (0.84-1.01)	829.62	5.51 (5.11-6.02)
Central Latin America	799.90	1.47 (1.40-1.57)	249.51	3.55 (3.33-3.80)	3536.97	6.50 (6.24-6.79)	2588.29	36.80 (35.11-38.54)	70.29	0.13 (0.12-0.14)	126.71	1.80 (1.71-1.89)
Central Sub-Saharan Africa	82.09	0.50 (0.32-0.91)	31.49	1.57 (1.06-2.86)	1044.56	6.32 (4.19-11.97)	779.44	38.79 (26.63-71.37)	21.19	0.13 (0.08-0.24)	31.39	1.56 (1.08-2.82)
East Asia	2411.69	0.59 (0.34-0.85)	1025.65	1.35 (0.89-2.04)	21351.35	5.23 (2.87-7.45)	18103.81	23.88 (15.28-37.15)	429.99	0.11 (0.06-0.15)	801.94	1.06 (0.69-1.65)
Eastern Europe	15793.63	21.96 (20.59-24.11)	10952.50	34.70 (32.19-38.26)	28145.98	39.14 (36.29-43.89)	25697.91	81.42 (75.84-89.39)	574.40	0.80 (0.74-0.90)	1143.57	3.62 (3.39-3.95)
Eastern Sub-Saharan Africa	911.70	1.58 (0.88-2.21)	195.30	3.23 (1.85-4.48)	10161.30	17.56 (9.69-24.73)	4676.52	77.24 (45.05-107.02)	195.30	0.34 (0.19-0.48)	190.26	3.14 (1.84-4.41)
High-income Asia Pacific	3787.70	6.60 (5.87-7.39)	3420.40	17.48 (15.61-19.49)	2993.34	5.22 (4.43-6.11)	3280.50	16.76 (15.19-18.50)	57.42	0.10 (0.09-0.12)	155.67	0.80 (0.71-0.88)

High-income North America	110312.33	122.00 (118.67-125.24)	91736.42	279.29 (259.14-290.94)	49550.96	54.80 (52.32-57.61)	48753.03	148.43 (137.98-156.33)	903.15	1.00 (0.98-1.02)	2180.29	6.64 (6.03-6.97)
North Africa and Middle East	2853.74	2.76 (1.18-4.31)	801.76	5.78 (2.80-8.48)	4488.98	4.34 (1.73-7.27)	3412.68	24.60 (10.99-36.35)	86.12	0.08 (0.03-0.14)	157.00	1.13 (0.49-1.63)
Oceania	1.92	0.09 (0.06-0.17)	0.44	0.19 (0.13-0.35)	29.41	1.45 (0.88-2.56)	13.35	5.78 (3.84-10.60)	0.52	0.03 (0.02-0.05)	0.70	0.30 (0.21-0.55)
South Asia	1362.16	0.41 (0.23-0.61)	300.08	0.67 (0.41-1.00)	12880.41	3.87 (2.23-6.00)	6240.53	13.85 (8.61-21.23)	249.96	0.08 (0.04-0.12)	255.03	0.57 (0.35-0.87)
Southeast Asia	301.83	0.19 (0.12-0.31)	100.05	0.44 (0.31-0.74)	4295.51	2.77 (1.69-4.52)	2790.54	12.39 (8.60-20.81)	85.17	0.05 (0.03-0.09)	126.26	0.56 (0.39-0.93)
Southern Latin America	981.07	6.17 (5.63-6.72)	495.64	11.30 (10.10-12.54)	2507.61	15.77 (14.64-17.00)	2710.81	61.82 (57.39-65.78)	50.59	0.32 (0.29-0.34)	129.43	2.95 (2.73-3.14)
Southern Sub-Saharan Africa	464.46	2.68 (1.70-4.07)	127.46	5.06 (2.97-8.08)	2762.91	15.96 (10.07-24.19)	1876.89	74.50 (43.75-115.73)	54.99	0.32 (0.20-0.49)	89.93	3.57 (2.05-5.43)
Tropical Latin America	1709.61	3.32 (3.14-3.53)	499.39	6.19 (5.64-6.71)	7365.71	14.31 (13.64-15.00)	4983.69	61.78 (57.63-65.28)	146.74	0.29 (0.27-0.30)	225.79	2.80 (2.59-2.96)
Western Europe	77635.15	65.25 (62.56-67.94)	70667.03	127.18 (119.27-133.67)	55484.57	46.63 (44.98-48.46)	69706.64	125.45 (117.42-131.09)	1077.84	0.91 (0.88-0.93)	3405.29	6.13 (5.63-6.42)
Western Sub-Saharan Africa	324.84	0.56 (0.22-0.80)	89.72	1.29 (0.66-1.70)	3472.02	5.98 (2.40-8.45)	2192.47	31.51 (16.12-41.80)	67.61	0.12 (0.05-0.16)	98.98	1.42 (0.76-1.88)

Abbreviations: SDI, Socio-demographic Index; UI, uncertainty interval; DALYs, disability-adjusted life-years.

Table 2. Estimated number of cases, DALYs, deaths, and age-standardized rates of prevalence (ASPR), DALYs (ASDR), and mortality (ASMR) for premenopausal and postmenopausal malignant melanoma in 2021 at the Global and Regional level

Characteristics	Prevalence				DALYs				Mortality				1990-2021	
	Premenopausal (age <55 years)		Postmenopausal (age ≥55 years)		Premenopausal (age <55 years)		Postmenopausal (age ≥55 years)		Premenopausal (age <55 years)		Postmenopausal (age ≥55 years)		AAPC of the ASPR (95% CI)	
	Cases	ASPR per 100,000 (95% UI)	Cases	ASPR per 100,000 (95% UI)	DALYs	ASDR per 100,000 (95% UI)	DALYs	ASDR per 100,000 (95% UI)	Deaths	ASMR per 100,000 (95% UI)	Deaths	ASMR per 100,000 (95% UI)	Premenopausal (age <55 years)	Postmenopausal (age ≥55 years)
Global	412490.42	16.53 (15.09-17.78)	640433.62	81.43 (74.33-87.03)	295121.02	11.83 (9.20-14.35)	441310.91	56.11 (48.79-63.66)	5727.02	0.23 (0.18-0.28)	21500.71	2.73 (2.36-3.07)	0.08 (0.07-0.09)	0.87 (0.83-0.91)
SDI quintiles														
High	254071.50	82.19 (79.42-85.22)	462282.88	250.68 (225.58-265.10)	88919.79	28.76 (27.10-30.78)	197920.40	107.33 (95.98-115.29)	1629.17	0.53 (0.51-0.54)	9854.26	5.34 (4.62-5.74)	0.45 (0.37-0.53)	3.07 (2.90-3.23)
High middle	106728.09	27.30 (23.84-30.37)	147880.05	78.70 (69.44-86.41)	73159.53	18.71 (15.88-21.68)	128685.84	68.49 (58.83-76.94)	1461.79	0.37 (0.32-0.44)	6263.85	3.33 (2.87-3.74)	0.46 (0.44-0.48)	1.48 (1.44-1.51)
Middle	34563.70	4.37 (2.87-5.68)	24817.89	10.08 (6.36-13.12)	56150.01	7.11 (4.68-9.36)	70907.27	28.81 (18.84-36.07)	1147.96	0.15 (0.10-0.19)	3449.61	1.40 (0.92-1.72)	0.11 (0.11-0.11)	0.26 (0.25-0.26)
Low middle	10693.61	1.66 (0.99-2.30)	3618.00	2.88 (1.96-3.74)	40728.53	6.34 (3.70-9.16)	26753.02	21.32 (13.97-30.13)	796.19	0.12 (0.07-0.18)	1201.86	0.96 (0.63-1.34)	0.04 (0.04-0.04)	0.06 (0.06-0.06)
Low	5968.46	1.66 (0.86-2.58)	1135.07	2.71 (1.46-4.01)	35812.95	9.94 (5.23-15.4)	16387.69	39.17 (21.20-58.44)	684.98	0.19 (0.10-0.29)	696.35	1.66 (0.90-2.48)	0.03 (0.03-0.03)	0.03 (0.03-0.03)
GBD Regions														
Andean Latin America	1086.98	4.97 (3.46-8.40)	1020.45	19.73 (13.78-27.73)	2070.86	9.46 (6.70-14.56)	3588.93	69.38 (50.29-95.42)	42.83	0.20 (0.14-0.30)	186.45	3.60 (2.61-4.81)	0.12 (0.11-0.13)	0.51 (0.49-0.54)
Australasia	18974.77	206.92 (182.11-233.05)	29643.17	639.84 (543.71-727.84)	6089.54	66.40 (59.05-74.55)	11674.37	251.99 (217.29-282.19)	108.50	1.18 (1.07-1.30)	584.94	12.63 (10.61-14.13)	-0.36 (-1.05-0.34)	2.01 (-0.21-4.24)
Caribbean	671.45	4.39 (3.62-5.23)	839.56	17.10 (14.57-20.23)	1289.86	8.43 (6.00-12.62)	1661.97	33.85 (28.46-41.51)	26.15	0.17 (0.12-0.25)	84.76	1.73 (1.46-2.05)	0.07 (0.06-0.08)	0.37 (0.34-0.40)
Central Asia	1372.30	4.46 (3.74-5.27)	1382.04	16.93 (14.33-19.65)	2531.96	8.23 (6.89-9.95)	3762.09	46.09 (39.94-52.96)	51.31	0.17 (0.14-0.20)	183.32	2.25 (1.96-2.57)	0.04 (0.03-0.05)	0.20 (0.17-0.24)
Central Europe	19551.13	59.77 (52.12-68.62)	29650.51	142.24 (124.37-161.22)	14825.91	45.32 (40.02-51.41)	32384.24	155.35 (138.75-173.22)	298.69	0.91 (0.81-1.03)	1749.39	8.39 (7.46-9.36)	1.23 (1.18-1.28)	3.37 (3.28-3.45)
Central Latin America	5767.00	6.70 (5.76-7.70)	4177.55	18.08 (15.70-20.78)	9712.98	11.28 (9.62-12.89)	12093.88	52.33 (46.29-58.59)	198.93	0.23 (0.20-0.26)	609.26	2.64 (2.29-2.93)	0.17 (0.17-0.18)	0.47 (0.45-0.49)
Central Sub-Saharan Africa	436.52	1.00 (0.61-2.11)	139.43	2.84 (1.65-5.54)	2917.83	6.72 (4.02-13.95)	2080.73	42.45 (25.01-81.37)	59.08	0.14 (0.08-0.28)	88.29	1.80 (1.06-3.38)	0.02 (0.02-0.02)	0.04 (0.04-0.04)
East Asia	17957.22	4.14 (1.68-6.73)	21154.13	10.45 (4.18-16.04)	28047.97	6.46 (2.67-9.98)	48089.69	23.76 (9.81-34.78)	592.52	0.14 (0.06-0.21)	2348.08	1.16 (0.48-1.66)	0.12 (0.11-0.12)	0.30 (0.29-0.30)
Eastern Europe	36145.47	59.05 (51.85-66.00)	52763.13	138.27 (124.39-151.32)	31820.53	51.98 (44.62-60.43)	54504.68	142.83 (128.49-158.65)	646.06	1.06 (0.91-1.23)	2504.42	6.56 (5.91-7.24)	1.12 (1.04-1.20)	3.42 (3.26-3.57)

Eastern Sub-Saharan Africa	4374.29	3.12 (1.54-5.54)	709.85	5.01 (2.62-8.10)	25957.74	18.54 (9.40-32.16)	10330.99	72.97 (38.46-115.43)	491.51	0.35 (0.18-0.60)	431.21	3.05 (1.62-4.77)	0.05 (0.05-0.05)	0.06 (0.06-0.06)
High-income Asia Pacific	9832.28	20.02 (16.13-23.28)	17301.77	45.36 (35.66-54.14)	3409.47	6.94 (5.63-8.01)	8073.92	21.17 (16.79-24.92)	61.89	0.13 (0.14-0.10)	470.12	1.23 (0.95-1.45)	0.45 (0.41-0.49)	0.87 (0.80-0.93)
High-income North America	102202.99	95.30 (91.62-99.57)	202483.16	336.11 (305.38-354.89)	32613.45	30.41 (28.39-33.03)	72737.26	120.74 (109.18-130.19)	584.17	0.54 (0.53-0.57)	3327.49	5.52 (4.80-5.92)	-0.96 (-1.14 - -0.78)	2.02 (1.66-2.37)
North Africa and Middle East	19877.41	9.86 (4.70-12.63)	15237.24	40.47 (16.94-53.19)	8258.77	4.10 (1.78-5.41)	8565.28	22.75 (9.25-28.60)	147.96	0.07 (0.03-0.10)	388.23	1.03 (0.40-1.29)	0.24 (0.23-0.24)	1.15 (1.13-1.17)
Oceania	4.68	0.11 (0.06-0.17)	1.16	0.20 (0.13-0.35)	68.15	1.54 (0.94-2.50)	34.04	5.79 (3.81-10.32)	1.20	0.03 (0.02-0.04)	1.88	0.32 (0.21-0.56)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
South Asia	8443.88	1.36 (0.74-2.27)	2662.56	2.10 (1.19-3.25)	30652.09	4.93 (2.80-8.20)	18543.46	14.65 (8.74-24.22)	590.73	0.10 (0.05-0.16)	797.75	0.63 (0.37-1.05)	0.03 (0.03-0.03)	0.05 (0.05-0.05)
Southeast Asia	1097.94	0.47 (0.29-0.73)	505.09	0.82 (0.49-1.30)	8334.03	3.59 (2.21-5.44)	8582.69	14.00 (8.40-21.08)	172.59	0.07 (0.05-0.11)	410.54	0.67 (0.40-1.03)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
Southern Latin America	4153.04	18.99 (17.03-21.11)	4003.59	49.20 (43.46-55.03)	4268.55	19.52 (17.80-21.35)	6435.36	79.08 (70.96-86.25)	84.80	0.39 (0.35-0.42)	330.17	4.06 (3.62-4.39)	0.42 (0.39-0.45)	1.29 (1.24-1.34)
Southern Sub-Saharan Africa	1404.48	5.13 (2.78-8.65)	641.53	11.27 (5.59-14.98)	6332.10	23.12 (11.93-34.40)	5451.91	95.74 (48.61-123.76)	129.55	0.47 (0.24-0.70)	251.92	4.42 (2.20-5.63)	0.07 (0.07-0.08)	0.20 (0.20-0.21)
Tropical Latin America	7490.06	9.93 (9.32-10.58)	4996.03	20.54 (18.45-22.30)	13557.80	17.97 (16.92-18.97)	16334.21	67.14 (60.31-71.84)	278.36	0.37 (0.35-0.39)	816.22	3.35 (2.94-3.63)	0.21 (0.20-0.23)	0.46 (0.44-0.48)
Western Europe	149709.02	124.01 (117.90-129.69)	250728.75	312.70 (277.70-335.38)	50990.02	42.24 (39.63-45.28)	110198.40	137.43 (121.74-149.02)	939.63	0.78 (0.75-0.81)	5664.54	7.06 (6.01-7.66)	1.92 (1.74-2.10)	6.01 (5.82-6.20)
Western Sub-Saharan Africa	1937.51	1.22 (0.30-1.96)	392.91	2.30 (0.84-3.30)	11371.38	7.16 (1.87-11.09)	6182.80	36.19 (13.69-50.96)	220.55	0.14 (0.04-0.21)	271.74	1.59 (0.63-2.19)	0.02 (0.02-0.02)	0.03 (0.03-0.03)

Abbreviations: SDI, Socio-demographic Index; UI, uncertainty interval; DALYs, disability-adjusted life-years; AAPC, average annual percentage change.

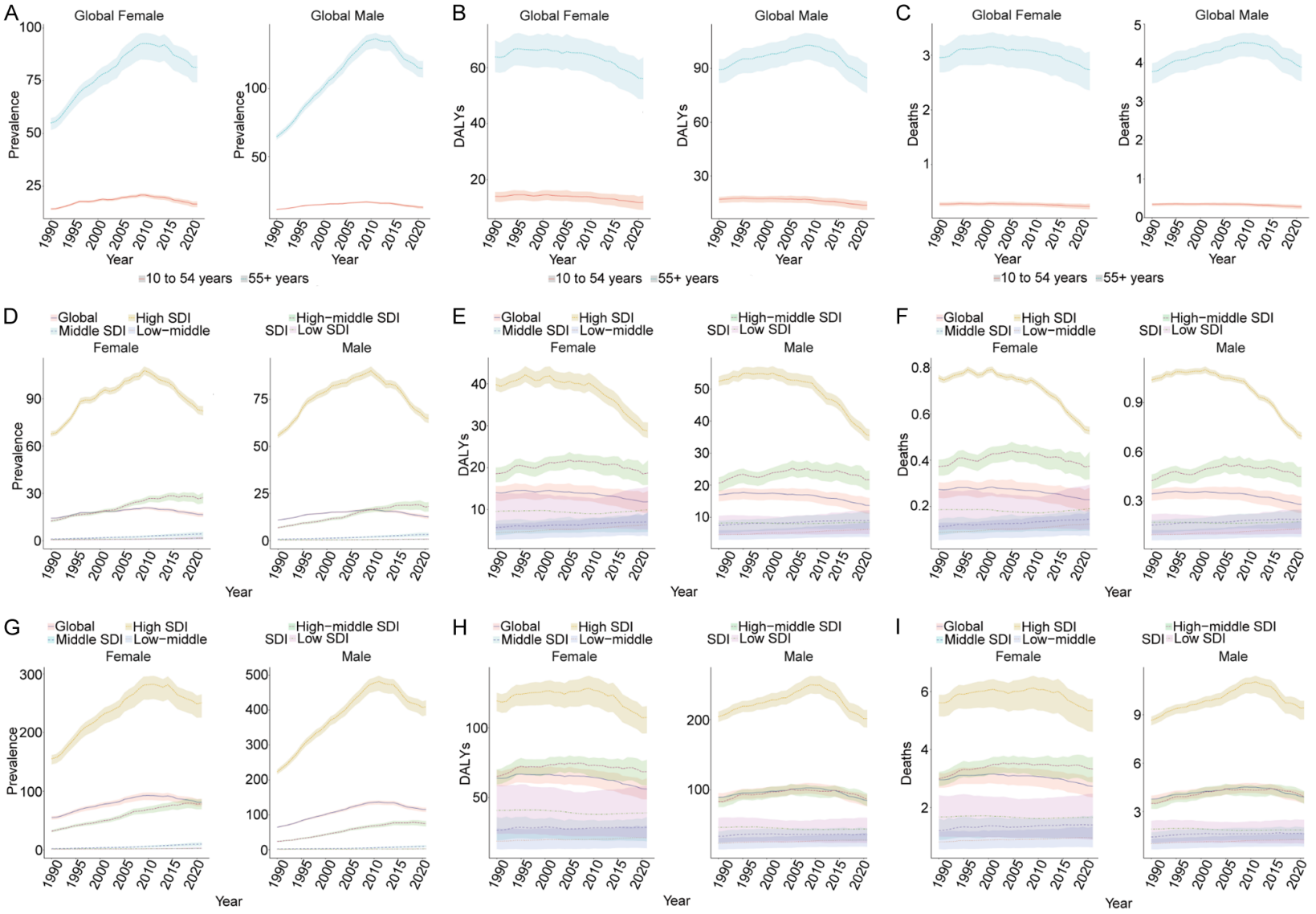

Figure 2. Trends in age-standardized prevalence, DALYs, and mortality rates for malignant melanoma in individuals aged 10-54 years and 55 years and older from 1990 to 2021 at the global level and across five SDI regions. Trends in age-standardized prevalence (A), DALYs (B), and mortality (C) rates for malignant melanoma in individuals aged 10-54 years and 55 years and older from 1990 to 2021 at the global level. Trends in age-standardized prevalence (D), DALYs (E), and mortality (F) rates for 10-54 years malignant melanoma from 1990 to 2021 across five SDI regions. Trends in age-standardized prevalence (G), DALYs (H), and mortality (I) rates for 55 years and older malignant melanoma from 1990 to 2021 across five SDI regions. DALYs, disability-adjusted life years; SDI, socio-demographic index.

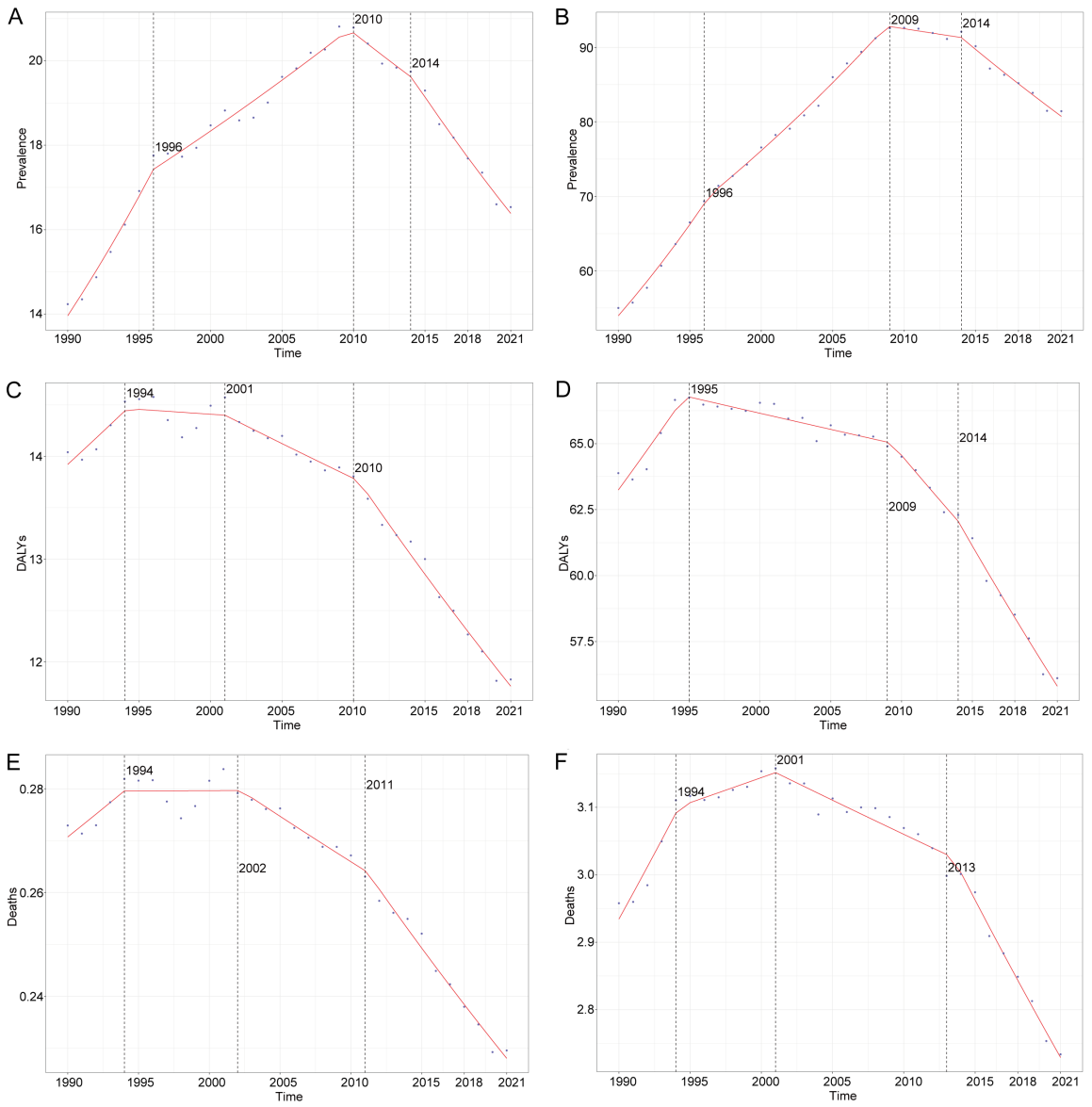

Figure 3. AAPC of age-standardized prevalence, DALYs, and mortality rates for premenopausal and postmenopausal malignant melanoma from 1990 to 2021. AAPC of age-standardized prevalence (A), DALYs (C), and mortality (E) rates for premenopausal malignant melanoma from 1990 to 2021. AAPC of age-standardized prevalence (B), DALYs (D), and mortality (F) rates for postmenopausal malignant melanoma from 1990 to 2021. AAPC>0 represented an increase in the rate, while AAPC<0 represented a decrease in the rate. AAPC, average annual percentage change; DALYs, disability-adjusted life years.

(-0.08 to -0.06)], and for ASMR it was -0.001% [95% CI (-0.002 to -0.001)] (**Figure 3C** and **3E**). Trend changes in ASDR occurred in 1994, 2001 and 2010. Between 1990 and 1994, ASDR gradually increased, with an APC of 0.92% [95% CI (0.44 to 1.41)]. From 1994 to 2001, ASDR remained relatively stable, with an APC of -0.07% [95% CI (-0.43 to 0.30)]. From 2001 to 2010, ASDR gradually declined, with an APC of -0.48% [95% CI (-0.65 to -0.32)], and from 2010 to 2021, the downward trend became more pronounced, with an APC of -1.46% [95% CI (-1.61 to -1.32)] (**Figure 3C**). Trend changes in ASMR occurred in 1994, 2002, and 2011. Between 1990 and 1994, ASMR slowly increased, with an APC of 0.81% [95% CI (0.08 to 1.55)]. From 1994 to 2002, ASMR remained relatively stable, with an APC of 0.003% [95% CI (-0.21 to 0.21)]. From 2002 to 2011, ASMR gradually declined, with an APC

Burden of pre- and post-menopausal malignant melanoma

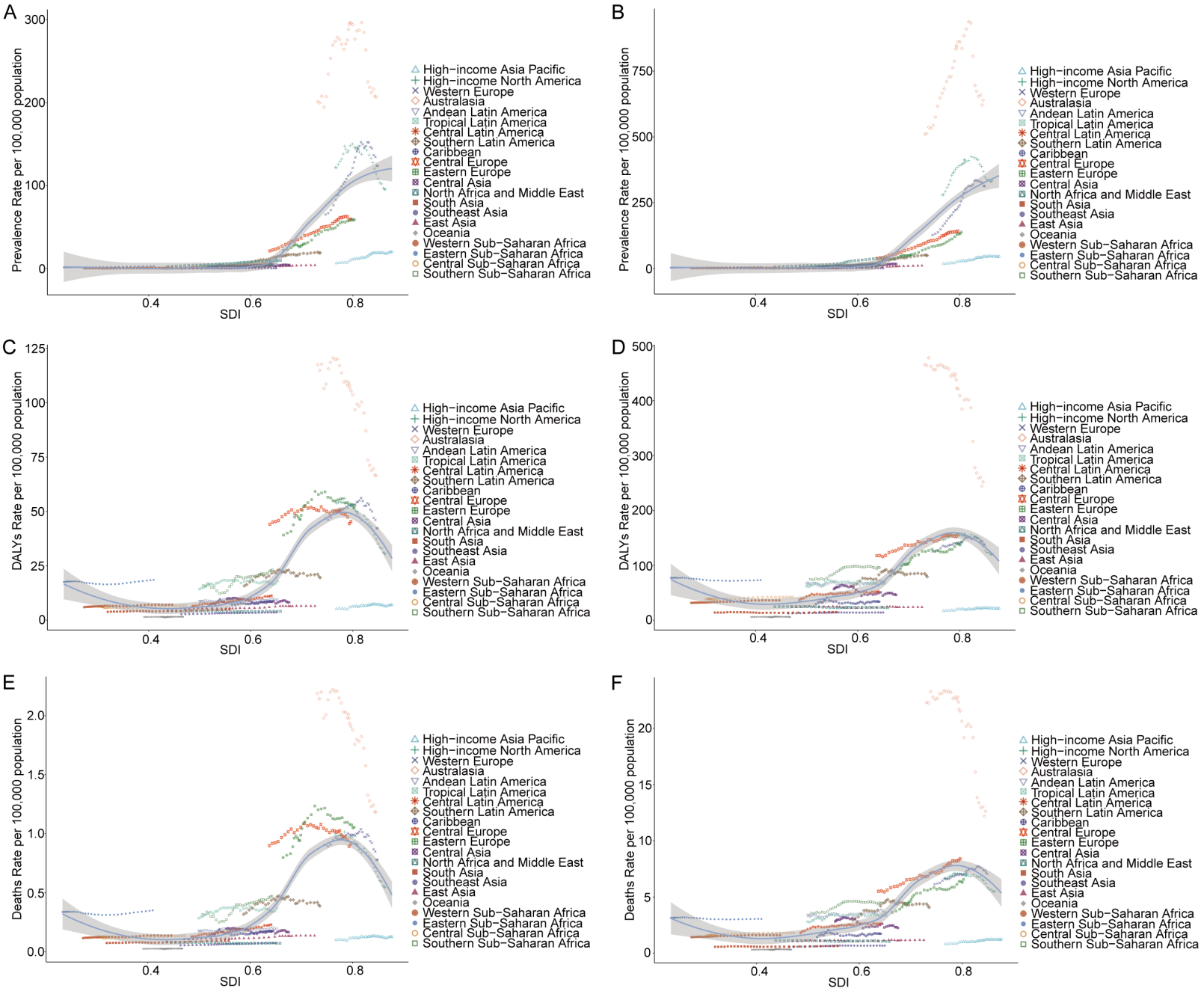

Figure 4. Trends in age-standardized prevalence, DALYs, and mortality rates for premenopausal and postmenopausal malignant melanoma from 1990 to 2021 across 21 GBD regions by SDI. Trends in age-standardized prevalence (A), DALYs (C), and mortality (E) rates for premenopausal malignant melanoma from 1990 to 2021 across 21 GBD regions by SDI. Trends in age-standardized prevalence (B), DALYs (D), and mortality (F) rates for postmenopausal malignant melanoma from 1990 to 2021 across 21 GBD regions by SDI. For each region, points from left to right depicted estimates from each year from 1990 to 2021. DALYs, disability-adjusted life years; SDI, socio-demographic index.

of -0.65% [95% CI (-0.85 to -0.44)], and from 2011 to 2021, the downward trend became more pronounced, with an APC of -1.47% [95% CI (-1.65 to -1.30)] (**Figure 3E**). From 1990 to 2021, the AAPC for ASDR of postmenopausal malignant melanoma was -0.24% [95% CI (-0.26 to -0.22)], and for ASMR it was -0.006% [95% CI (-0.007 to -0.005)] (**Figure 3D** and **3F**). Trend changes in ASDR occurred in 1995, 2009 and 2014. Between 1990 and 1995, ASDR significantly increased, with an APC of 1.17% [95% CI (0.84 to 1.50)]. From 1995 to 2009, ASDR declined slowly, with an APC of -0.19% [95% CI (-0.25 to -0.12)]. From 2009 to 2014, the decline became more pronounced, with an APC of -0.98% [95% CI (-1.44 to -0.52)], and from 2014 to 2021, the decline further intensified, with an APC of -1.51% [95% CI (-1.66 to -1.35)] (**Figure 3D**). Trend changes in ASMR occurred in 1994, 2001 and 2013. Between 1990 and 1994, ASMR significantly increased, with an APC of 1.31% [95% CI (0.99 to 1.64)]. From 1994 to 2001, ASMR remained relatively stable, with an APC of 0.24% [95% CI (-0.002 to 0.48)]. From 2001 to 2013, ASMR gradually declined, with an APC of -0.33% [95% CI (-0.40 to -0.25)], and from 2013 to 2021, the downward trend became more pronounced, with an APC of -1.36% [95% CI (-1.51 to -1.21)] (**Figure 3F**).

Among the five SDI regions, the high SDI region in pre- and post-menopausal groups exhibited the highest ASDR and ASMR values. However, a decreasing trend has recently been observed. In 2021, the ASDR in the high SDI region was 28.76 [95% UI (27.10, 30.78)] for the premenopausal group and 107.33 [95% UI (95.98, 115.29)] for the postmenopausal group, while the ASMR was 0.53 [95% UI (0.51, 0.54)] for the premenopausal group and 5.34 [95% UI (4.62, 5.74)] for the postmenopausal group. This was followed by high-middle SDI region, with both indicators being higher than the world average. In contrast, the low-middle SDI region had the lowest ASDR and ASMR (**Table 2** and **Figure 2E**, **2F**, **2H**, **2I**).

In the 21 regions, Australasia had the highest ASDR and ASMR in the premenopausal and postmenopausal groups, although these rates have declined significantly in recent years. In 2021, the ASDR in Australasia was 66.40 [95% UI (59.05, 74.55)] for the premenopausal group and 251.99 [95% UI (217.29, 282.19)] for the postmenopausal group, while the ASMR was 1.18 [95% UI (1.07, 1.30)] for the premenopausal group and 12.63 [95% UI (10.61, 14.13)] for the postmenopausal group (**Table 2**). Other high SDI regions, including High-income North America and Western Europe, exhibited ASDR and ASMR comparable to those of high-middle SDI regions, such as Central Europe and Eastern Europe (**Figure 4B**, **4C**, **4E**, **4F**).

The global maps of ASPR, ASDR, and ASMR for pre- and post-menopausal malignant melanoma in 2021 were presented in **Figure 5A-F**. At the national level, New Zealand exhibited the highest ASPR for the premenopausal group, recorded at 245.63 [95% UI (209.56, 279.91)]. Meanwhile, the postmenopausal group also exhibited the highest ASPR in New Zealand, at 909.37 [95% UI (754.63, 1037.39)] (**Figure 5A** and **5D**). Furthermore, New Zealand reported the highest ASDR and ASMR for pre- and postmenopausal groups, respectively (**Figure 5B**, **5C**, **5E**, **5F**).

Decomposition analysis

We conducted a decomposition analysis to explore how population, aging, and epidemiological changes affect the burden of malignant melanoma in women. Globally, the population was the major driver of the increase in prevalence from 1990 to 2021, accounting for 48.0% of the rise. Meanwhile, epidemiological change and aging contributed 25.2% and 26.8%, respectively. In the high SDI region, population was the most significant factor for the increase in prevalence, whereas in the other four SDI regions, epidemiological change was the main positive contributor (**Figure 6A**).

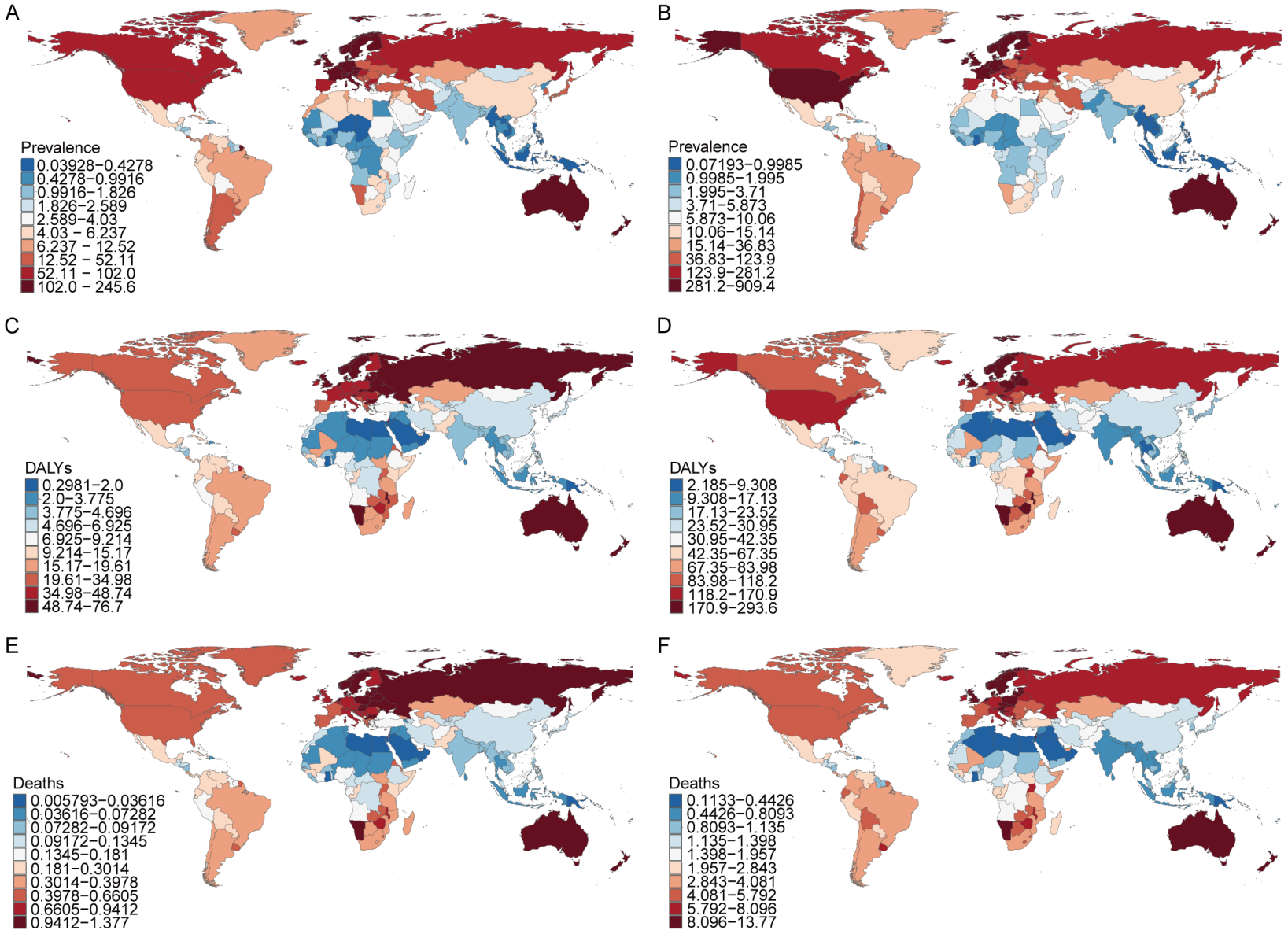

Figure 5. The global map of age-standardized prevalence, DALYs, and mortality rates, attributable to malignant melanoma in premenopausal and postmenopausal females across 204 countries and territories. Age-standardized prevalence (A), DALYs (C), and mortality (E) rates for premenopausal malignant melanoma in 2021 at the national level. Age-standardized prevalence (B), DALYs (D), and mortality (F) rates for postmenopausal malignant melanoma in 2021 at the national level. DALYs, disability-adjusted life years.

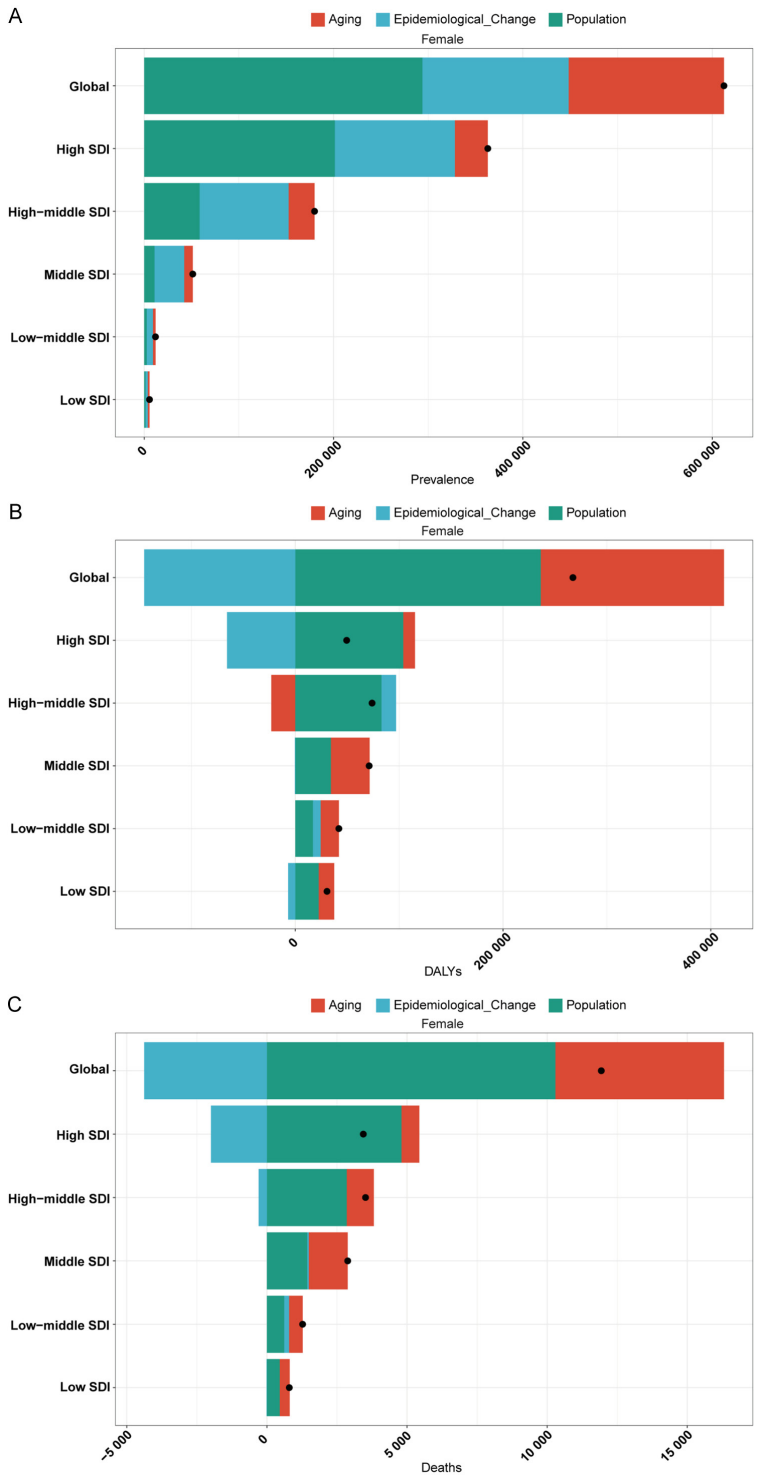

Figure 6. Changes in prevalence (A), DALYs (B), and deaths (C) of malignant melanoma in female according to population-level determinants of aging, epidemiological change, and population growth from 1990 to 2021 at the global level and by SDI quintile. The black dot represents the combined effect of all three components. For individual component, the magnitude of a positive value indicates a corresponding increase in malignant melanoma indicator attributed to the component, while the magnitude of a negative value indicates a corresponding decrease in malignant melanoma indicator attributed to the component. DALYs, disability-adjusted life years; SDI, socio-demographic index.

Population was also the main driver of the increase in global DALYs from 1990 to 2021, contributing 88.43%. This was followed by aging, with a contribution of 65.97%, while epidemiological change had a negative contribution of -54.4%. The contribution of population to overall DALYs was most pronounced in the high SDI, high middle SDI, and low SDI regions. Contrary to the global profile, aging exhibited a negative contribution in the high-middle SDI region, whereas epidemiological change had a positive contribution (**Figure 6B**).

Globally, population was the primary contributor to the increase in deaths, accounting for 86.27%, followed by aging with a contribution of 50.42%. In contrast, epidemiological change had a negative contribution of -36.69%. Similarly, the deaths of malignant melanoma in females were driven primarily by population across all five SDI regions (**Figure 6C**).

Discussion

Our study is the first to investigate the burden of malignant melanoma by menopausal status. Sex hormones are generally considered to be associated with the development and prognosis of hormone-dependent tumors such as breast, ovarian, and endometrial cancers [21]. However, increasing studies have recently identified an association between sex hormones and malignant melanoma. Regarding morbidity, a younger age at menarche and an older age at menopause are associated with an increased risk of malignant melanoma in women [22]. During pregnancy, estrogen level rise rapidly, and malignant

melanoma is the most common malignancy among pregnant and postpartum women, accounting for 31% of all malignancies during pregnancy and 24% during lactation [23]. Furthermore, using exogenous estrogen replacement therapy in postmenopausal women is a risk factor for an elevated risk of malignant melanoma (relative risk [RR], 1.32; 95% CI, 1.17-1.49) [24]. Regarding prognosis, a diagnosis of malignant melanoma during pregnancy is linked to a higher risk of cause-specific mortality (hazard ratio [HR], 1.52; 95% CI, 1.01-2.31; $P = 0.047$) [23]. Additionally, women who had given birth in the year preceding their malignant melanoma diagnosis have a mortality rate twice that of other female patients (HR, 2.06; 95% CI, 1.42-3.01) [25]. Consistent with these findings, our study also found that the prevalence of malignant melanoma was higher in women than in men aged <55 years and lower in women than in men aged ≥55 years, suggesting that high estrogen levels may be among the risk factors for malignant melanoma in women.

Unlike tissues such as the breast (primarily express estrogen receptor (ER) α), skin tissue and malignant melanoma lesions predominantly express ERβ, which is generally associated with inhibition of cell proliferation [26]. In women, ERβ expression in the skin decreases with age and declines rapidly after menopause [27]. A comparative study exhibited that ERβ expression is negatively correlated with Breslow thickness, which is an important prognostic factor for malignant melanoma [28]. Based on these findings, we hypothesize that estrogen may not directly affect tumor cells but rather influences the immune system, thereby promoting the development of malignant melanoma in premenopausal women.

A recent study has revealed that the skin is not merely a simple physical barrier but is rich in various immune cells capable of autonomously producing antibodies that modulate host-microbiota interactions [29]. This suggests that the skin may function as an independent immune system with significant potential. Estrogen has been demonstrated to regulate the function of various immune cells [30, 31]. The ERβ signaling pathway in T cells can attenuate autoimmune diseases by suppressing inflammatory T-cell responses. This is achieved through increased expression of Forkhead Box P3 (FOXP3), promotion of Treg proliferation, inhibition of CD4+ and CD8+ cell infiltration, and suppression of cytotoxic cytokines such as IFN-γ, interleukin (IL)-17, and iNOS production [32, 33]. In NK cells, estrogen/medroxyprogesterone hormone replacement therapy in healthy postmenopausal women decreased NK cytotoxicity and reduced IL-2 and IFN-γ synthesis [34]. Besides, estrogen induces granzyme B inhibitors, which attenuate NK cell-mediated apoptosis [35]. In dendritic cells, the ERβ pathway mitigates experimental autoimmune encephalomyelitis by inhibiting TNF-α production [36].

Due to its high immunogenicity, malignant melanoma was the first cancer type for which the FDA approved the use of immune checkpoint inhibitors (ICIs). However, a meta-analysis has exhibited that ICIs are significantly more effective in male cancer patients compared to female patients (HR, 0.85; 95% CI, 0.77-0.94; $P = 0.0019$) [33]. Chakraborty et al. reported that in a murine model of malignant melanoma, estrogen promotes the polarization of tumor-associated macrophages toward the immune-suppressive M2 phenotype, leading to CD8+ T cell dysfunction and exhaustion, and induces resistance to ICIs. Meanwhile, the selective estrogen receptor downregulator, fulvestrant, has been demonstrated to enhance the antitumor efficacy of ICIs [5]. Artham et al. demonstrated that estrogen facilitates the growth of malignant melanoma and breast cancer by reducing the number of eosinophils in peripheral and tumor-associated tissues while also inhibiting their antitumor activity. Furthermore, they found that the antitumor efficacy of ICIs was enhanced when combined with the estrogen receptor inhibitor lasofoxifene [6]. Our study found that from 1990 to 2021, the declines in ASDR and ASMR for premenopausal malignant melanoma were smaller than those for postmenopausal malignant melanoma. This suggests that premenopausal patients with malignant melanoma may still lack effective treatment options. Therefore, it is worth exploring whether combining estrogen receptor inhibitors with ICIs can improve the prognosis for this cohort. However, further preclinical and clinical trials are needed to test this hypothesis, as the GBD database does not provide information on patient medication use. More-

over, it is crucial to balance the side effects of treatment with patients' reproductive needs.

In summary, estrogen plays a complex and critical role in developing malignant melanoma and in modulating antitumor immunity. Given the significant decline in estrogen levels after menopause, comparing the burden of malignant melanoma between premenopausal and postmenopausal women provides crucial insights into the role of estrogen in tumor development and progression. Consequently, this study employed comprehensive data from the GBD database to investigate the global burden of malignant melanoma in women of different menopausal statuses. The greater disease burden observed in premenopausal women compared to age-matched men underscores the necessity of enhancing melanoma screening efforts specifically for premenopausal women. Changes in hormone levels during pregnancy often lead to pigmentation, which can be difficult to distinguish from malignant melanoma lesions. Additionally, the maternal immune system tends to adopt an immune-tolerant state during pregnancy, and increased lymphangiogenesis may facilitate tumor metastasis [37]. As a result, increased vigilance for malignant melanoma during pregnancy is warranted for clinicians.

Consistent with previous research, our study identified significant regional inequalities in the burden of malignant melanoma [38]. The burden was notably higher among women in high SDI regions, particularly Australasia, which can be attributed to factors such as high UV exposure, predominantly Caucasian ethnicity, and effective cancer screening and registration systems [39-42]. However, recently, a decreasing trend in ASPR has been observed in these regions, likely due to an increased awareness of disease prevention. Conversely, the ASPR in high-middle SDI regions has steadily increased, indicating the need for enhanced preventive and curative measures against malignant melanoma. Given that malignant melanoma is rare and progresses rapidly, the absence of advanced diagnostic techniques, such as dermoscopy, in low SDI regions may result in misdiagnosis and mistreatment, potentially contributing to the low ASPR observed in these regions [43].

This study has several limitations. First, this study is highly dependent on data from the GBD database. Due to the lack of comprehensive data collection and reporting systems in developing countries, some disease burden data may be missing. Second, since cancer registries typically do not routinely collect information on patients' menopausal status, we defined menopausal status using a unified age range instead of individual-level data. This classification method may lead to unavoidable misclassification in some cases. Third, the GBD database lacks data on the pathological subtypes of malignant melanoma, which differ in malignancy and clinical prognosis. Finally, the GBD database does not provide information related to hormone replacement therapy and ovarian function suppression therapy, which affect hormone levels.

Conclusion

The risk and prognosis of malignant melanoma in women may vary according to menopausal status, potentially due to the complex effects of sex hormones on the immune system. Therefore, further studies are essential to develop screening and treatment guidelines for women with different levels of sex hormone in different SDI regions.

Acknowledgements

We gratefully acknowledge the support to this study by the Key R&D plan of the Ministry of Science and Technology (2023YFC2505900) and the National Natural Science Foundation of China (82222054, 82471811, 82071799).

Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Address correspondence to: Yanfang Liu and Jianming Zheng, Department of Pathology, The First Affiliated Hospital of Naval Medical University, Shanghai 200433, China. E-mail: Liuyanfang002-15@163.com (YFL); jmzheng1962@163.com (JMZ); Liqiang Hao, Department of Colorectal Surgery, The First Affiliated Hospital of Naval Medical University, Shanghai 200433, China. E-mail: hao_liqiang@163.com; Meng Guo, National Key Laboratory of

Immunity and Inflammation and Institute of Immunology, Naval Medical University, Shanghai 200433, China. E-mail: guom@immunol.org

References

[1] Whiteman DC, Pandeya N and Olsen CM. Differences in mean age at diagnosis of invasive melanoma for men and women, by anatomic site, thickness, and subtype. Br J Dermatol 2024; [Epub ahead of print].

[2] Liu-Smith F and Ziogas A. Age-dependent interaction between sex and geographic ultraviolet index in melanoma risk. J Am Acad Dermatol 2020; 82: 1102-1108, e1103.

[3] Boniol M, Autier P, Boyle P and Gandini S. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. BMJ 2012; 345: e4757.

[4] Lee JJ, Jung YL, Cheong TC, Espejo Valle-Inclan J, Chu C, Gulhan DC, Ljungström V, Jin H, Viswanadham VV, Watson EV, Cortés-Ciriano I, Elledge SJ, Chiarle R, Pellman D and Park PJ. ERα-associated translocations underlie oncogene amplifications in breast cancer. Nature 2023; 618: 1024-1032.

[5] Chakraborty B, Byemerwa J, Shepherd J, Haines CN, Baldi R, Gong W, Liu W, Mukherjee D, Artham S, Lim F, Bae Y, Brueckner O, Tavares K, Wardell SE, Hanks BA, Perou CM, Chang CY and McDonnell DP. Inhibition of estrogen signaling in myeloid cells increases tumor immunity in melanoma. J Clin Invest 2021; 131: e151347.

[6] Artham S, Juras PK, Goyal A, Chakraborty P, Byemerwa J, Liu S, Wardell SE, Chakraborty B, Crowder D, Lim F, Strawser CH, Newlin M, Racioppi A, Dent S, Mirminachi B, Roper J, Perou CM, Chang CY and McDonnell DP. Estrogen signaling suppresses tumor-associated tissue eosinophilia to promote breast tumor growth. Sci Adv 2024; 10: eadp2442.

[7] Stevens GA, Alkema L, Black RE, Boerma JT, Collins GS, Ezzati M, Grove JT, Hogan DR, Hogan MC, Horton R, Lawn JE, Marušić A, Mathers CD, Murray CJ, Rudan I, Salomon JA, Simpson PJ, Vos T and Welch V; (The GATHER Working Group). Guidelines for accurate and transparent health estimates reporting: the GATHER statement. Lancet 2016; 388: e19-e23.

[8] Patel KK, Qavi AJ, Hock KG and Gronowski AM. Establishing reference intervals for hCG in postmenopausal women. Clin Biochem 2017; 50: 234-237.

[9] Kamp E, Ashraf M, Musbahi E and DeGiovanni C. Menopause, skin and common dermatoses. Part 1: hair disorders. Clin Exp Dermatol 2022; 47: 2110-2116.

[10] Strand NH, D'Souza RS, Gomez DA, Whitney MA, Attanti S, Anderson MA, Moeschler SM, Chadwick AL and Maloney JA. Pain during menopause. Maturitas 2025; 191: 108135.

[11] Kuang Z, Wang J, Liu K, Wu J, Ge Y, Zhu G, Cao L, Ma X and Li J. Global, regional, and national burden of tracheal, bronchus, and lung cancer and its risk factors from 1990 to 2021: findings from the global burden of disease study 2021. EClinicalMedicine 2024; 75: 102804.

[12] Zhang K, Kan C, Han F, Zhang J, Ding C, Guo Z, Huang N, Zhang Y, Hou N and Sun X. Global, regional, and national epidemiology of diabetes in children from 1990 to 2019. JAMA Pediatr 2023; 177: 837-846.

[13] Pu Y, He L, Wang X, Zhang Y, Zhao S and Fan J. Global, regional, and national levels and trends in burden of urticaria: a systematic analysis for the global burden of disease study 2019. J Glob Health 2024; 14: 04095.

[14] Jang H, Park S, Kim MS, Yon DK, Lee SW, Koyanagi A, Kostev K, Shin JI and Smith L. Global, regional and national burden of alopecia areata and its associated diseases, 1990-2019: a systematic analysis of the global burden of disease study 2019. Eur J Clin Invest 2023; 53: e13958.

[15] Zhang Y, Dong S, Ma Y and Mou Y. Burden of psoriasis in young adults worldwide from the global burden of disease study 2019. Front Endocrinol (Lausanne) 2024; 15: 1308822.

[16] Wang R, Li Z, Liu S and Zhang D. Global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019: a systematic analysis based on the global burden of disease study 2019. BMJ Open 2023; 13: e065186.

[17] Lv B, Lan JX, Si YF, Ren YF, Li MY, Guo FF, Tang G, Bian Y, Wang XH, Zhang RJ, Du ZH, Liu XF, Yu SY, Tian CL, Cao XY and Wang J. Epidemiological trends of subarachnoid hemorrhage at global, regional, and national level: a trend analysis study from 1990 to 2021. Mil Med Res 2024; 11: 46.

[18] Yang K, Yang X, Jin C, Ding S, Liu T, Ma B, Sun H, Zhang J and Li Y. Global burden of type 1 diabetes in adults aged 65 years and older, 1990-2019: population based study. BMJ 2024; 385: e078432.

[19] Ruan R, Liu X, Zhang Y, Tang M, He B, Zhang QW and Shu T. Global, regional, and national advances toward the management of rheumatic heart disease based on the global burden of disease study 2019. J Am Heart Assoc 2023; 12: e028921.

[20] Wu Z, Xia F and Lin R. Global burden of cancer and associated risk factors in 204 countries and territories, 1980-2021: a systematic analysis for the GBD 2021. J Hematol Oncol 2024; 17: 119.

[21] Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and

breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol 2012; 13: 1141-1151.
[22] Kvaskoff M, Bijon A, Mesrine S, Boutron-Ruault MC and Clavel-Chapelon F. Cutaneous melanoma and endogenous hormonal factors: a large French prospective study. Am J Epidemiol 2011; 173: 1192-1202.
[23] Stensheim H, Møller B, van Dijk T and Fosså SD. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. J Clin Oncol 2009; 27: 45-51.
[24] Tang X, Zhang H, Cui Y, Wang L, Wang Z, Zhang Y, Huo J, Cai J, Rinaldi G, Bhagavathula AS and Xiaopeng Y. Postmenopausal exogenous hormone therapy and Melanoma risk in women: a systematic review and time-response meta-analysis. Pharmacol Res 2020; 160: 105182.
[25] Møller H, Purushotham A, Linklater KM, Garmo H, Holmberg L, Lambe M, Yallop D and Devereux S. Recent childbirth is an adverse prognostic factor in breast cancer and melanoma, but not in Hodgkin lymphoma. Eur J Cancer 2013; 49: 3686-3693.
[26] Hall G and Phillips TJ. Estrogen and skin: the effects of estrogen, menopause, and hormone replacement therapy on the skin. J Am Acad Dermatol 2005; 53: 555-568; quiz 569-572.
[27] de Giorgi V, Gori A, Alfaioli B, Papi F, Grazzini M, Rossari S, Lotti T and Massi D. Influence of sex hormones on melanoma. J Clin Oncol 2011; 29: e94-95; author reply e96.
[28] de Giorgi V, Gori A, Gandini S, Papi F, Grazzini M, Rossari S, Simoni A, Maio V and Massi D. Oestrogen receptor beta and melanoma: a comparative study. Br J Dermatol 2013; 168: 513-519.
[29] Gribonika I, Band VI, Chi L, Perez-Chaparro PJ, Link VM, Ansaldo E, Oguz C, Bousbaine D, Fischbach MA and Belkaid Y. Skin autonomous antibody production regulates host-microbiota interactions. Nature 2024; [Epub ahead of print].
[30] Hoffmann JP, Liu JA, Seddu K and Klein SL. Sex hormone signaling and regulation of immune function. Immunity 2023; 56: 2472-2491.
[31] Xiao T, Lee J, Gauntner TD, Velegraki M, Lathia JD and Li Z. Hallmarks of sex bias in immuno-oncology: mechanisms and therapeutic implications. Nat Rev Cancer 2024; 24: 338-355.
[32] Goodman WA, Bedoyan SM, Havran HL, Richardson B, Cameron MJ and Pizarro TT. Impaired estrogen signaling underlies regulatory T cell loss-of-function in the chronically inflamed intestine. Proc Natl Acad Sci U S A 2020; 117: 17166-17176.
[33] Conforti F, Pala L, Bagnardi V, De Pas T, Martinetti M, Viale G, Gelber RD and Goldhirsch A. Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol 2018; 19: 737-746.
[34] Stopińska-Głuszak U, Waligóra J, Grzela T, Głuszak M, Jóźwiak J, Radomski D, Roszkowski PI and Malejczyk J. Effect of estrogen/progesterone hormone replacement therapy on natural killer cell cytotoxicity and immunoregulatory cytokine release by peripheral blood mononuclear cells of postmenopausal women. J Reprod Immunol 2006; 69: 65-75.
[35] Jiang X, Orr BA, Kranz DM and Shapiro DJ. Estrogen induction of the granzyme B inhibitor, proteinase inhibitor 9, protects cells against apoptosis mediated by cytotoxic T lymphocytes and natural killer cells. Endocrinology 2006; 147: 1419-1426.
[36] Du S, Sandoval F, Trinh P, Umeda E and Voskuhl R. Estrogen receptor-β ligand treatment modulates dendritic cells in the target organ during autoimmune demyelinating disease. Eur J Immunol 2011; 41: 140-150.
[37] Carter TJ, George C, Harwood C and Nathan P. Melanoma in pregnancy: diagnosis and management in early-stage and advanced disease. Eur J Cancer 2022; 166: 240-253.
[38] Liu C, Liu X, Hu L, Li X, Xin H and Zhu S. Global, regional, and national burden of cutaneous malignant melanoma from 1990 to 2021 and prediction to 2045. Front Oncol 2024; 14: 1512942.
[39] Gordon LG, Rodriguez-Acevedo AJ, Køster B, Guy GP Jr, Sinclair C, Van Deventer E and Green AC. Association of indoor tanning regulations with health and economic outcomes in North America and Europe. JAMA Dermatol 2020; 156: 401-410.
[40] Kolitz E, Lopes FCPS, Arffa M, Pineider J, Bogucka R and Adamson AS. UV exposure and the risk of keratinocyte carcinoma in skin of color: a systematic review. JAMA Dermatol 2022; 158: 542-546.
[41] Work Group; Invited Reviewers; Kim JYS, Kozlow JH, Mittal B, Moyer J, Olenecki T and Rodgers P. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol 2018; 78: 560-578.
[42] Gao DX, Swetter SM, Hawryluk EB, Geller AC and Beaulieu D. Screening motivations among participants of the American Academy of Dermatology's SPOT skin cancer screening program from 2018 to 2019: a cross-sectional analysis. J Am Acad Dermatol 2023; 88: 674-676.
[43] Elmore JG, Barnhill RL, Elder DE, Longton GM, Pepe MS, Reisch LM, Carney PA, Titus LJ, Nelson HD, Onega T, Tosteson ANA, Weinstock MA, Knezevich SR and Piepkorn MW. Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study. BMJ 2017; 357: j2813.

Table S1. GBD 2021 standard population structure

Age Group	Percent of Population	Rounded
Early Neonatal	0.0396232	0.04
Late Neonatal	0.117777	0.12
1 to 5 months	0.864776	0.86
6 to 11 months	1.01009	1.01
12 to 23 months	2.01613	2.02
2 to 4	5.9934	5.99
5 to 9	9.65824	9.66
10 to 14	8.99361	8.99
15 to 19	8.28913	8.29
20 to 24	7.80122	7.8
25 to 29	7.59144	7.59
30 to 34	7.32171	7.32
35 to 39	6.82805	6.83
40 to 44	6.14735	6.15
45 to 49	5.51133	5.51
50 to 54	4.91312	4.91
55 to 59	4.34586	4.35
60 to 64	3.68223	3.68
65 to 69	2.98509	2.99
70 to 74	2.26526	2.27
75 to 79	1.59758	1.6
80 to 84	1.09729	1.1
85 to 89	0.604519	0.6
90 to 94	0.246663	0.25
95 plus	0.0785092	0.08