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ORIGINAL RESEARCH

Worldwide cancer statistics of adolescents and young adults in 2019: a systematic analysis of the Global Burden of Disease Study 2019

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Background: The cancer burden in adolescents and young adults (AYAs) deserves more attention. However, global cancer statistics for AYAs are often presented as aggregates, concealing important heterogeneity. This study aimed to describe the worldwide profile of cancer incidence, mortality, and corresponding trends from 1990 to 2019 among 15-39-year olds by focusing on the patterns by age, sex, sociodemographic index (SDI), and regions.

Patients and methods: Global, regional, and country data on the number of cancer cases and cancer-related deaths for 29 cancer types were collected from the 2019 Global Burden of Disease (GBD) Study. We also summarized the results using five levels of the SDI and 21 GBD regions.

Results: In 2019, an estimated 1 335 100 new cancer cases and 397 583 cancer-related deaths occurred among AYAs worldwide. While the incidence rate increased mildly, the death rate decreased significantly between 1990 and 2019, with an estimated annual percentage change of 0.38 (95% confidence interval 0.36-0.39) and −0.93 (95% confidence interval −0.95 to −0.92), respectively. The cancer burden was disproportionally greater among women than among men. The cancer profiles varied substantially across geographical regions, with the highest burden being in South Asia and East Asia. Besides, the cancer incidence in the high SDI regions was four times higher than that in the low SDI regions; however, the mortality burden in the high SDI region was lower than that in the low SDI region, which reflected the differences in cancer profiles across SDI regions and the inferior outcomes in the low SDI regions.

Conclusion: This study updates the previous epidemiological data of the cancer burden of AYAs. The cancer burden in AYAs varied substantially according to age, sex, SDI, and geographical regions. These findings highlight that the specific cancer profile of AYA patients requires targeted cancer control measures to reduce the cancer burden in this age group.

Key words: cancer burden, adolescents and young adults, incidence, death, trend

INTRODUCTION

The burden of cancer is distributed unequally across age groups. Cancers in adolescents and young adults (AYAs) have been defined by the National Cancer Institute as diagnoses occurring between the ages of 15 and 39.[1] A growing body of evidence shows that cancers in AYAs have distinct features, in terms of the distribution of cancer types, cancer biology, risk factors, prognosis, and survivorship, compared with that of cancers diagnosed in other age groups.[2-5] Although the overall incidence of cancer in AYAs is lower than that in older adults, the loss of healthy years of life is disproportionately higher in AYAs.[6,7] Compared with older patients with cancer, AYAs with cancer have a higher risk of long-term effects, such as infertility, organ dysfunction, and secondary cancers.[8-10] Thus the cancer burden of AYAs may lead to a decline in productivity growth and social structure. An accurate profile of the global cancer burden in AYAs is needed to direct health care policies and improve cancer-associated outcomes.

The global burden of cancer among AYAs is often ignored by cancer researchers and has rarely been studied in depth. Research on cancers in AYAs has mainly been conducted in high sociodemographic index (SDI) countries, especially the United States and several European countries, and seldom

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in countries with limited resources.[2,11-13] Although Fidler et al.[6] first described the global cancer profile of young adults in 2012 using data from GLOBOCAN 2012, the pattern of the cancer burden among AYAs has changed dramatically in the last decade. Subsequently, Trama et al.[3] summarized the epidemiological data of the cancer burden of AYAs in 2018, but the data source, Population Based Cancer Registries, for this study covered only a small fraction of the populations living in low- and middle-income countries.

In this study, we collected epidemiological data, including incidence and mortality by sex, age, SDI, region, and country, on AYA cancers between 1990 and 2019 from the Global Burden of Disease (GBD) 2019 Study. Thereafter, we calculated the estimated annual percentage changes (EAPCs) to assess the trends of incident and death rates. An accurate evaluation of the worldwide burden and trends of AYA cancers will help to inform policy development and enhance service delivery.

METHODS

Data source and collection

The GBD study was conducted by the Institute for Health Metrics and Evaluation (IHME), which provides a systematic scientific assessment of disease and injury incidence, prevalence, and mortality. The GBD 2019 Study provides a comprehensive epidemiologic estimation of the burden of 369 diseases and injuries in 204 countries and territories from 1990 to 2019.[14] IHME's general approach to the GBD 2019 Study and its major improvements over previous cycles have been explained in the previous publications.[14]

As the features of cancers in AYAs are distinct from those in the younger and older groups, different classification systems may uncover additional unique features. We investigated the incidence, mortality, and corresponding trends of the 29 cancer types that were included in the GBD 2019 Study: bladder cancer; brain and central nervous system (CNS) cancer; breast cancer; cervical cancer; colon and rectum cancer (referred to as colorectal cancer); esophageal cancer; gallbladder and biliary tract cancer; Hodgkin's lymphoma; kidney cancer; larynx cancer; leukemia; lip and oral cavity cancer; liver cancer; tracheal, bronchus, and lung cancer (referred to as lung cancer); malignant skin melanoma; mesothelioma; multiple myeloma; nasopharynx cancer; non-Hodgkin's lymphoma; nonmelanoma skin cancer; other pharynx cancers; ovarian cancer; pancreatic cancer; prostate cancer; stomach cancer; testicular cancer; thyroid cancer; uterine cancer; and other malignant neoplasms.

To assess the cancer burden of AYAs, global, regional, and country and territory estimates of the number of cancer cases and cancer-related deaths that occurred from 1990 to 2019 were collected from the GBD 2019 Study. To analyze the variations across age groups, the incidence and death rates among individuals aged 0-14 years, 15-39 years, 40 years and older were also extracted.

The SDI, as a composite indicator of a country's lag-distributed income per capita, average years of schooling, and the fertility rate in females under the age of 25 years, is developed by GBD researchers. It is the geometric mean of 0 to 1 indices of total fertility rate under the age of 25, mean education for those aged 15 and older, and lag distributed income per capita. As a composite, a location with an SDI of 0 would have a theoretical minimum level of development relevant to health, while a location with an SDI of 1 would have a theoretical maximum level. According the value of SDI, all countries are classified into low SDI (0-0.454743), low—middle SDI (0.454743-0.607679), middle SDI (0.607679-0.689504), high—middle SDI (0.689504-0.805129), and high SDI (0.805129-1) categories (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2021.100255). According to a geographical hierarchy, the GBD 2019 Study data were grouped into 21 regions, and the variations in the cancer burden in these regions were analyzed. In addition, the incidence and death rates of all cancers in different SDI and geographical regions were described.

Statistical analysis

EAPCs were used to assess the trends in cancer incidence and death rates, which were calculated using a regression model. The whole process includes two steps. Step 1: linear regression of 30 years' data; that is, $y = \alpha + \beta x + \varepsilon$, where $y = \ln$ (rate), $x =$ calendar year, and ε was the error term. Step 2: Calculation of linear regression parameters. EAPC $=$ $100 \times [\exp(\beta) - 1]$.[15,16] All the calculations were performed using R software (version 3.6.3). All the tests were two-tailed. A 95% confidence interval (CI) for each quantity was used for the analyses. The statistical significance was set at $P < 0.05$.

Ethics approval

This study was approved by an independent ethics committee of The First Affiliated Hospital, College of Medicine, Zhejiang University.

Consent for publication. Not applicable.

RESULTS

Overview of the cancer burden

Worldwide, it was estimated that there were 1 335 100 [95% uncertainty interval (UI) 1 243 397-1 426 785] new cancer cases and 397 583 (95% UI 371 460-426 061) cancer-related deaths among AYAs in 2019, with a female : male ratio of 1.35 for incidence and 1.04 for mortality (Tables 1 and 2). The incidence rate was 44.99 and the death rate was 13.39 cancer-associated deaths per 100 000 people per year in 2019 (Tables 1 and 2). While the incidence rate increased mildly, the death rate decreased significantly from 1990 to 2019, with the EAPC being 0.38 (95% UI 0.36-0.39) and −0.93 (95% CI −0.95 to 0.92), respectively

Table 1. Worldwide incidence and rates by sex for the 29 cancer types in 2019 among 15-39-year olds and the change in the trends from 1990 to 2019

	Both sexes		Female		Male		1990-2019 EAPC, No. (95% CI)
	Cases	Rate per 100 000	Cases	Rate per 100 000	Cases	Rate per 100 000	
Total cancers	1 335 100	44.99	766 692	52.32	568 407	37.82	0.38 (0.36 to 0.39)
Breast	169 859	5.72	168 775	11.51	1083	0.07	0.90 (0.87 to 0.93)
Nonmelanoma skin cancer	140 718	4.74	81 053	5.53	59 664	3.97	0.83 (0.79 to 0.86)
Cervical cancer	119 258	4.01	119 258	8.13	—	—	0.02 (0.01 to 0.05)
Leukemia	101 206	3.41	44 636	3.04	56 570	3.76	−0.49 (−0.53 to −0.46)
Colorectal cancer	76 089	2.56	29 258	1.99	46 831	3.11	1.22 (1.17 to 1.27)
Brain and central nervous system cancer	61 510	2.07	28 318	1.93	33 192	2.20	0.76 (0.76 to 0.80)
Testicular cancer	57 400	1.93	—	—	57 400	3.81	1.28 (1.22 to 1.33)
Non-Hodgkin's lymphoma	52 426	1.76	19 154	1.30	33 272	2.21	0.50 (0.44 to 0.54)
Stomach	49 007	1.65	21 125	1.44	27 882	1.85	−1.21 (−1.25 to −1.16)
Thyroid	46 832	1.57	34 545	2.35	12 285	0.81	1.77 (1.71 to 1.83)
Malignant skin melanoma	37 265	1.25	21 251	1.45	16 014	1.06	0.57 (0.51 to 0.63)
Ovarian cancer	35 831	1.20	35 831	2.44	—	—	0.89 (0.82 to 0.95)
Hodgkin's lymphoma	33 387	1.12	15 297	1.04	18 090	1.20	−0.36 (−0.42 to −0.30)
Lung	32 600	1.09	127 721	0.87	19 828	1.31	−1.13 (−1.19 to −1.07)
Lip and oral cavity	29 440	0.99	12 255	0.83	17 184	1.14	0.95 (0.88 to 1.02)
Nasopharynx	28 562	0.96	8359	0.57	20 202	1.34	1.68 (1.60 to 1.76)
Liver	25 429	0.85	6079	0.41	19 350	1.28	−3.51 (−3.57 to −3.45)
Kidney	21 135	0.71	8468	0.57	12 667	0.84	2.02 (1.93 to 2.11)
Uterine cancer	19 415	0.65	19 415	1.32	—	—	0.64 (0.56 to 0.72)
Bladder	14 095	0.47	3415	0.23	10 679	0.71	0.86 (0.75 to 0.96)
Pancreatic cancer	9401	0.31	3279	0.22	6121	0.40	0.56 (0.44 to 0.69)
Esophageal cancer	8087	0.27	2829	0.19	5258	0.34	−0.99 (−1.11 to −0.88)
Other pharynx cancer	7102	0.23	2622	0.17	4480	0.29	1.13 (0.98 to 1.28)
Prostate	5471	0.18	—	—	5471	0.36	2.13 (1.94 to 2.31)
Larynx	4214	0.14	1155	0.07	3059	0.20	−0.63 (−0.80 to −0.45)
Gallbladder and biliary tract	3841	0.12	1974	0.13	1866	0.12	−0.21 (−0.39 to −0.03)
Multiple myeloma	2930	0.09	1096	0.07	1834	0.12	0.95 (0.72 to 1.18)
Mesothelioma	1466	0.04	710	0.05	756	0.05	−0.90 (−1.18 to −0.61)
Other malignant neoplasms	141 110	4.75	63 752	4.35	77 357	5.14	0.79 (0.76 to 0.82)

CI, confidence interval; EAPC, estimated annual percentage change.

(Tables 1 and 2, Supplementary Data File S1, available at https://doi.org/10.1016/j.esmoop.2021.100255). Female predominance was a hallmark of the cancer burden in AYAs. The incidence rate of all cancers in females was 38.3% higher than that in males (52.32 versus 37.82 per 100 000). The cancers of the breast (11.51/100 000) and cervix (8.13/100 000) affected 37.6% of female patients (Table 1, Supplementary Data File S1, available at https://doi.org/10.1016/j.esmoop.2021.100255), while hematological malignancies, including leukemia (3.76/100 000), Hodgkin's lymphoma (1.20/100 000), and non-Hodgkin's lymphoma (2.21/100 000), accounted for the majority of cancers in males (Table 1, Supplementary Data File S1, available at https://doi.org/10.1016/j.esmoop.2021.100255).

Heterogeneity of cancer types

The burden varied greatly between the 29 types of cancer. The top five ranking cancer types overall in terms of new cases were breast cancer (5.72/100 000), nonmelanoma skin cancer (4.74/100 000), cervical cancer (4.01/100 000), leukemia (3.41/100 000), and colorectal cancer (2.56/100 000), with leukemia (1.51/100 000), breast cancer (1.45/100 000), brain and CNS cancer (0.98/100 000), colorectal cancer (0.95/100 000), and stomach cancer (0.93/100 000) being the main contributors to cancer-associated deaths among AYAs (Tables 1 and 2, Supplementary Data File S1, available at https://doi.org/10.1016/j.esmoop.2021.100255). The analysis of the long-term trends by cancer types showed that rising incidence rates in AYAs were driven mainly by the increased detection of breast cancer, nonmelanoma skin cancer, colorectal cancer, brain and CNS cancer, testicular cancer, and thyroid cancer (Figure 1A, Table 1, Supplementary Table S1A, available at https://doi.org/10.1016/j.esmoop.2021.100255). Cancer death rates in AYAs declined steadily since 2000, which was mainly due to the reduced mortality with leukemia, stomach cancer, lung cancer and liver cancer, with EAPCs of −1.58 (95% CI −1.63 to −1.54), −2.12 (95% CI −2.18 to −2.06), −1.38 (95% CI −1.45 to −1.31), and −3.98 (95% CI −4.05 to −3.91), respectively (Figure 1B, Table 2, Supplementary Table S1B, available at https://doi.org/10.1016/j.esmoop.2021.100255). Notably, these trends indicated the improvements in cancer surveillance, detection, and treatment in recent years.

Breast cancer and cervical cancer were the most frequent cancer types in AYAs for most countries in terms of incidence in 2019, accounting for 169, 859 (12.7%), and 119 258 (8.9%) of the total new cases, respectively (Figure 2A, Table 1, Supplementary Table S2A, available at https://doi.org/10.1016/j.esmoop.2021.100255). Other cancers with a high incidence included testicular cancer

Table 2. Worldwide deaths and rates by sex for the 29 cancer types in 2019 among 15–39-year olds and the change in the trends from 1990 to 2019

	Both sexes		Female		Male		1990-2019 EAPC, No. (95% CI)
	Cases	Rate per 100 000	Cases	Rate per 100 000	Cases	Rate per 100 000	
Total cancers	397 583	13.39	203 011	13.85	194 571	12.94	−0.93 (−0.95 to −0.92)
Leukemia	45 105	1.51	18 862	1.28	26 242	1.74	−1.58 (−1.63 to −1.54)
Breast	43 087	1.45	42 742	2.91	345	0.02	−0.10 (−0.15 to −0.04)
Brain and central nervous system cancer	29 105	0.98	11 947	0.81	17 158	1.14	−0.29 (−0.35 to −0.22)
Colorectal cancer	28 351	0.95	11 466	0.78	16 885	1.12	−0.10 (−0.17 to −0.03)
Stomach	27 895	0.93	12 923	0.88	14 971	0.99	−2.12 (−2.18 to −2.06)
Cervical cancer	27 168	0.91	27 168	1.85	—	—	−0.81 (−0.87 to −0.74)
Lung	24 771	0.83	9462	0.64	15 308	1.01	−1.38 (−1.45 to −1.31)
Non-Hodgkin's lymphoma	20 797	0.70	7608	0.51	13 188	0.87	−0.18 (−0.25 to −0.10)
Liver	18 572	0.62	4381	0.29	14 190	0.94	−3.98 (−4.05 to −3.91)
Lip and oral cavity	10 043	0.33	3609	0.24	6433	0.42	0.68 (0.55 to 0.80)
Ovarian cancer	8895	0.29	8895	0.60	—	—	0.39 (0.26 to 0.52)
Hodgkin's lymphoma	8093	0.27	3231	0.22	4861	0.32	−1.58 (−1.69 to −1.46)
Pancreatic cancer	7608	0.25	2593	0.17	5015	0.33	0.51(0.37 to 0.65)
Esophageal cancer	6214	0.20	2059	0.14	4154	0.27	−1.24 (−1.37 to −1.11)
Nasopharynx	6079	0.20	1901	0.12	4178	0.27	−2.15 (−2.28 to −2.02)
Testicular cancer	5352	0.18	—	—	5352	0.35	−0.04 (−0.19 to 0.12)
Other pharynx cancer	4359	0.14	1537	0.10	2822	0.18	0.72 (0.54 to 0.91)
Malignant skin melanoma	4248	0.14	1972	0.13	2275	0.15	−0.92 (−1.09 to −0.76)
Kidney	4016	0.13	1423	0.09	2592	0.17	0.90 (0.70 to 1.09)
Thyroid	2852	0.09	1774	0.12	1078	0.07	−0.10 (−0.31 to 0.11)
Gallbladder and biliary tract	2389	0.08	1280	0.08	1109	0.07	−0.46 (−0.68 to −0.23)
Larynx	2249	0.07	630	0.04	1619	0.10	−1.23 (−1.45 to −1.00)
Bladder	2050	0.06	631	0.04	1418	0.09	−1.00 (−1.24 to −0.76)
Uterine cancer	1808	0.06	1808	0.12	—	—	−1.66 (−1.89 to −1.42)
Multiple myeloma	1680	0.05	627	0.04	1053	0.07	0.47 (0.18 to 0.77)
Nonmelanoma skin cancer	1466	0.04	559	0.03	906	0.06	−0.34 (−0.63 to −0.05)
Mesothelioma	990	0.03	466	0.03	523	0.03	−0.79 (−1.14 to −0.43)
Prostate	875	0.02	—	—	875	0.05	−0.01 (−0.4 to 0.38)
Other malignant neoplasms	51 453	1.73	21 445	1.46	30 007	1.99	−0.04 (−0.09 to 0.01)

CI, confidence interval; EAPC, estimated annual percentage change.

[57 400 (4.3%); rate 1.93/100 000 people per year], leukemia [101 206 (7.6%); rate 3.41/100 000 people per year], and malignant skin melanoma [37 265 (2.8%); rate 1.25 per 100 000 people per year]. The top five ranking cancer types for most countries in terms of mortality were leukemia [45 105 (11.3%); rate 1.51 per 100 000 people per year], breast cancer [43 087 (10.8%); rate 1.45 per 100 000 people per year], brain and CNS cancer [29 105 (7.3%); rate 0.98 per 100 000 people per year], cervical cancer [27 168 (6.8%); rate 0.91 per 100 000 people per year], and liver cancer [18 572 (4.6%); rate 0.62 per 100 000 people per year] (Figure 2B and Table 2, Supplementary Table S2B, available at https://doi.org/10.1016/j.esmoop.2021.100255).

Age-specific burden

The cancer burden of AYAs was significantly higher than that of children (0-14 years old), with a 4.6 times greater burden for incidence and 4.0 times greater burden for deaths; however, it was significantly lower than that in patients aged 40 years or older (Figure 3, Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100255). The spectrum of cancers occurring among AYAs was also distinct from those diagnosed in younger or older age groups. The most frequent cancer types in children were leukemia, brain and CNS cancer, testicular cancer, and non-Hodgkin's lymphoma, the incidence of which decreased gradually with increasing age in AYAs and accounted for a small proportion in the older age group (Figure 3, Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100255). Breast cancer (ranked first for new cases and second for deaths overall), cervical cancer (ranked third for new cases and sixth for deaths overall), colorectal cancer (ranked fifth for new cases and fourth for deaths overall), and stomach cancer (ranked ninth for new cases and fifth for deaths overall) were observed more frequently among AYAs than among children. Nonmelanoma skin cancer (ranked second for new cases and twenty-sixth for deaths overall) was observed more frequently among young adults than among children or adolescents, though to a lesser extent than that observed in older adults (Tables 1 and 2, Figure 3A, Supplementary Table S3A, available at https://doi.org/10.1016/j.esmoop.2021.100255). In addition, even among AYAs, the cancer characteristics of incident cases varied according to the age interval of 5 years (Supplementary Table S3A, available at https://doi.org/10.1016/j.esmoop.2021.100255). The proportion of leukemia, brain and CNS cancer, testicular cancer, non-Hodgkin's lymphoma, and Hodgkin's lymphoma cases decreased with increasing age, whereas the proportions of breast cancer, cervical cancer, colorectal cancer, stomach cancer, and lung cancer cases increased (Figure 3A,

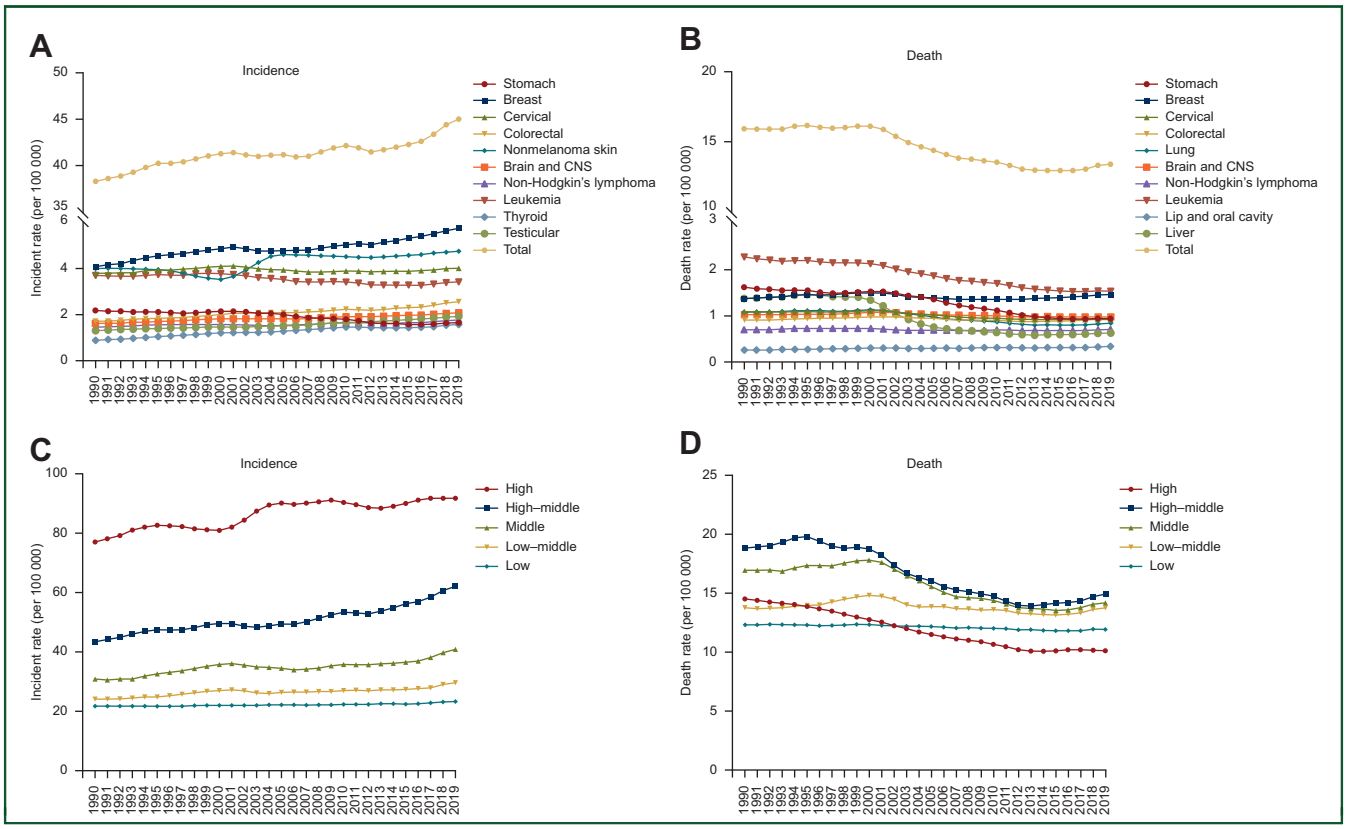

Figure 1. Worldwide trends of incidence and death rate by cancer type and SDI quintile among 15-39-year olds from 1990 to 2019.
(A) Top 10 cancer types in terms of incidence; (B) top 10 cancer types in terms of death rates; (C) incidence rates in different SDI quintiles; (D) death rates in different SDI quintiles.
CNS, central nervous system; SDI, sociodemographic index.

Supplementary Table S3A, available at https://doi.org/10.1016/j.esmoop.2021.100255). A similar transition was observed in deaths, except that the mortality rate of nonmelanoma skin cancer was low because of its good prognosis (Figure 3B, Supplementary Table S3B, available at https://doi.org/10.1016/j.esmoop.2021.100255).

Variations according to SDI levels

The SDI-based regional analysis showed that the burden of cancer in AYAs was higher in low SDI regions than in high SDI regions. Although the incidence of cancer in the high SDI regions was approximately 4.0 times greater than that in the low SDI regions (rates, 91.81 versus 23.21 per 100 000 people per year), the mortality burden in the high SDI region was lower than that in the low SDI region (rates, 10.10 versus 11.97 per 100 000 people per year; Figure 1C and D, Tables 3 and 4, Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100255). In addition, the EAPC analysis showed a significant decreasing trend for death rates in the high to the middle SDI regions. The analysis revealed that in the high SDI regions, the EAPC was −1.47 (95% CI −1.49 to −1.45); the high—middle SDI regions, −1.37 (95% CI −1.38 to −1.35); and in the middle SDI regions, −1.02 (95% CI −1.04 to −1.01). No obvious changes were observed in the low SDI regions (EAPC, −0.16; 95% CI −0.18 to −0.14) and in the low—middle SDI regions (EAPC, −0.20; 95% CI −0.22 to −0.18) (Figure 1D, Table 4, Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100255). These findings indicated that the global burden of cancer in AYAs varied across SDI regions and was disproportionally greater in the low- and low—middle SDI regions than in other regions.

With regard to cancer profile across the SDI regions, the top five cancer incident or mortality cases accounted for >40% of the total of new incident or mortality cases across all the SDI regions (Figure 4, Supplementary Data File S2, available at https://doi.org/10.1016/j.esmoop.2021.100255). Cervical cancer, breast cancer, and leukemia were all in the top five cancers in terms of incidence of cases across all the SDI regions, except for the high SDI region. In the high SDI regions, the most frequent cancer type was skin cancer, including nonmelanoma skin cancer (29.9%, rate 27.47 per 100 000 people per year) and skin melanoma (7.3%, rate 6.70 per 100 000 people per year; Figure 4, Supplementary Data File S2, available at https://doi.org/10.1016/j.esmoop.2021.100255). Notably, cervical cancer was the most frequently diagnosed cancer in the low SDI and low—middle SDI regions, while it ranked third, fifth, and eighth in the middle, high—middle, and high SDI regions, respectively. With respect to mortality, leukemia, brain and CNS cancer, and breast cancer were among the five leading causes of cancer-related deaths across all the SDI levels. Cervical and stomach cancers were the remaining leading causes of cancer death in the low and low—middle SDI

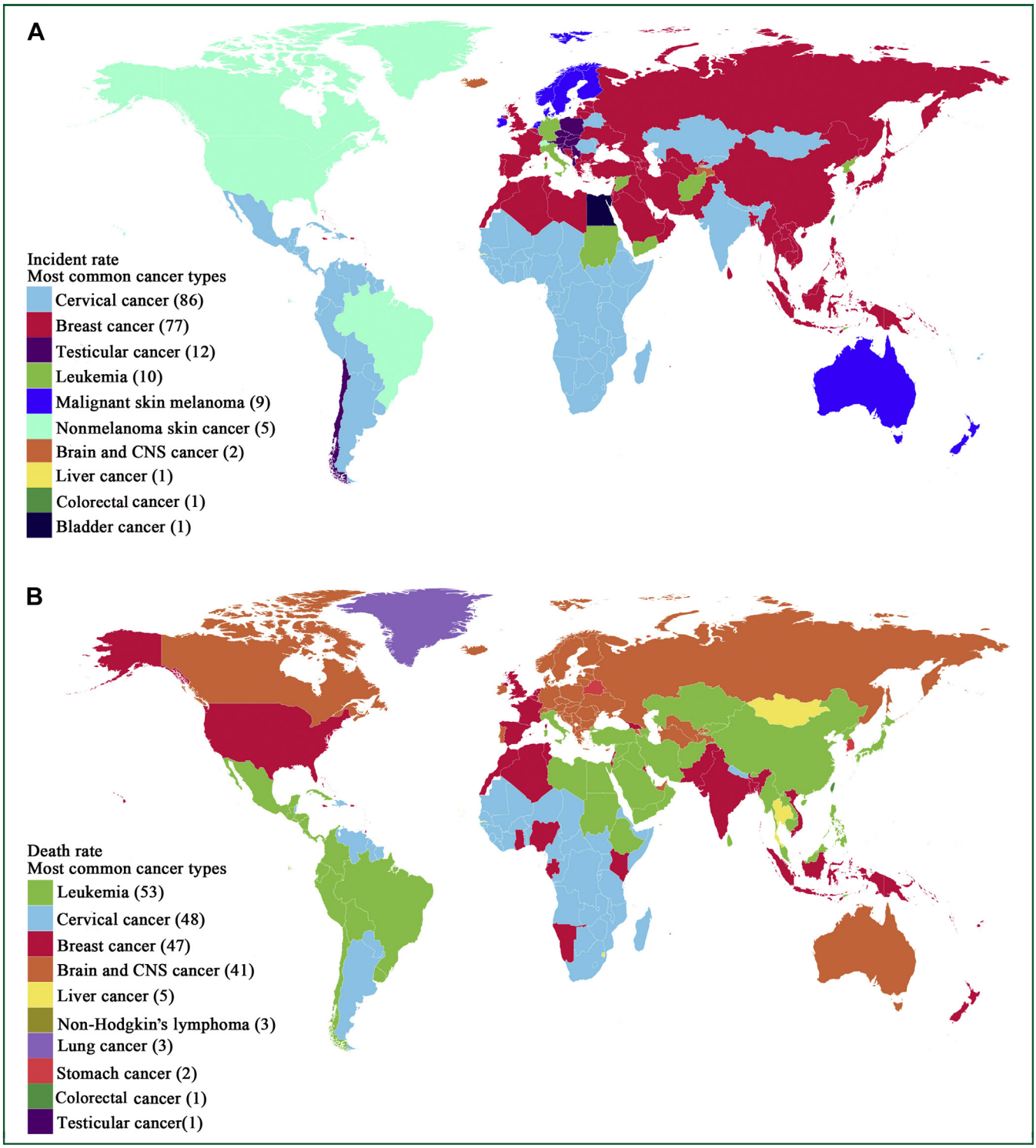

Figure 2. Global map of the most common cancer type by country in terms of (A) incidence cases and (B) cancer-related death cases among 15-39-year olds in 2019. Numbers in brackets are the number of countries where this type of cancer is the most common.
CNS, central nervous system.

regions, while colorectal and lung cancers were the remaining largest contributors to the mortality burden in the middle, high—middle, and high SDI regions (Figure 4, Supplementary Data File S2, available at https://doi.org/10.1016/j.esmoop.2021.100255).

Geographical differences

Based on the data in the 21 GBD regions over the last three decades, the incidence rates among AYAs was the greatest in the developed regions (especially in the high-

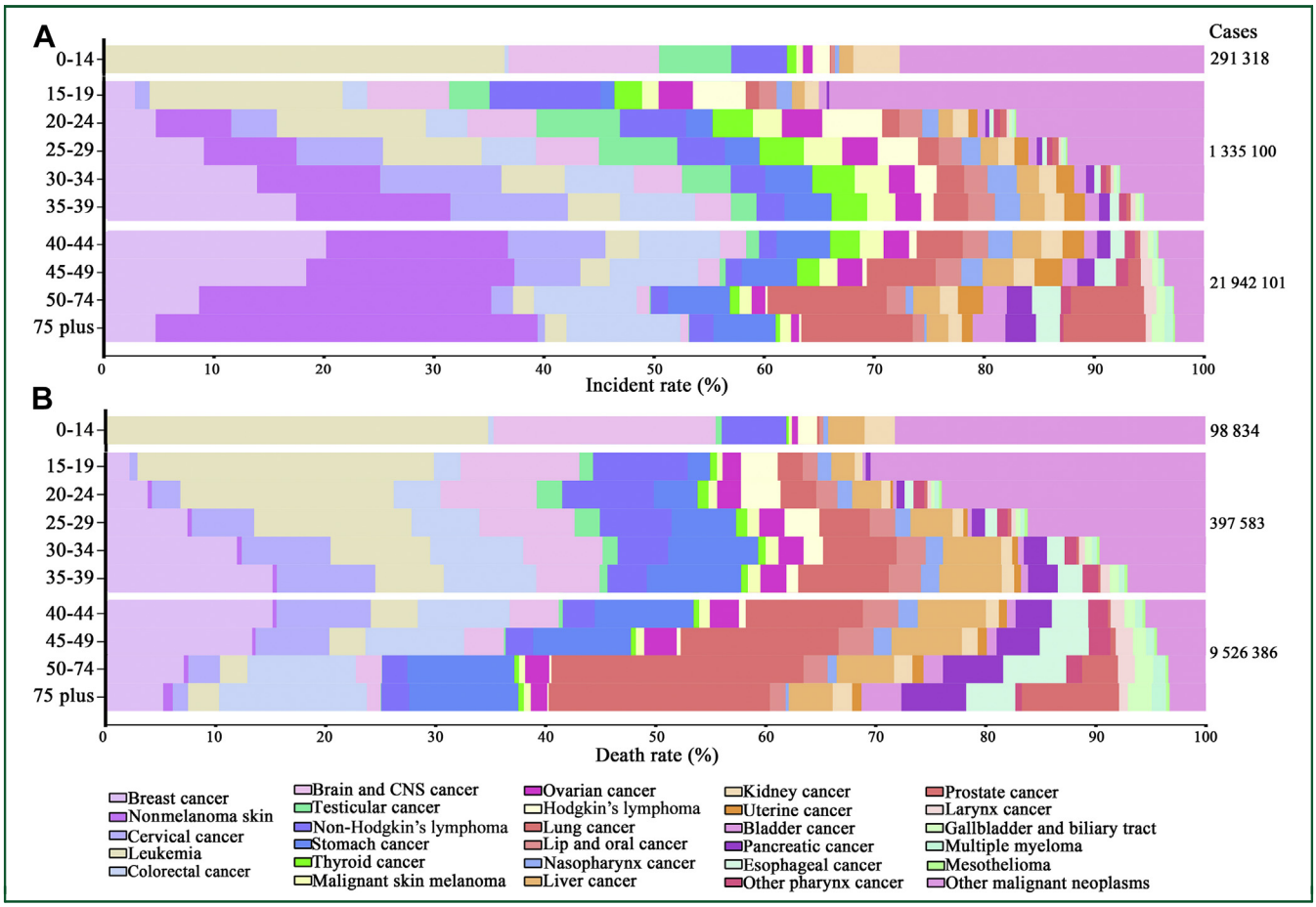

Figure 3. Worldwide distribution of cancer type by (A) age group and incidence, and (B) death cases in 2019.
CNS, central nervous system.

income regions of North America, Australasia, and Western Europe), whereas Africa and parts of Asia (south Asia and southeast Asia) had the lowest incidence rates (Figure 5A). The EAPC analysis showed a downward trend of incidence in four GBD regions (most parts of Africa and Central Asia) and an upward trend of incidence in the other 17 GBD regions (Table 3, Supplementary Table S5A, available at https://doi.org/10.1016/j.esmoop.2021.100255). A significant upward trend of incidence was observed in four regions, including North Africa and the Middle East (1.47 per 100 000 people per year), East Asia (1.47 per 100 000 people per year), Central Latin America (1.04 per 100 000 people per year), and tropical Latin America (1.00 per 100 000 people per year; Table 3). Although the incidence rate was the highest in the developed countries, these regions conversely had the lowest death rate (Figure 5, Tables 3 and 4, Supplementary Data File S3, available at https://doi.org/10.1016/j.esmoop.2021.100255). The top three lowest mortality burdens were in high-income North America, high-income Asia Pacific, and Western Europe, coinciding with the regions with the most significant decrease in EAPC, −1.56 (95% CI −1.57 to −1.54), −1.96 (95% CI −1.98 to −1.94), and −1.56 (95% CI −1.58 to −1.54; Table 4, Supplementary Table S5B, available at https://doi.org/10.1016/j.esmoop.2021.100255).

Additionally, cancer profiles varied substantially across the geographical regions. For instance, the incidence rate for breast cancer varied from 2.4 per 100 000 people per year in Eastern Sub-Saharan Africa to 11.1 per 100 000 people per year in Western Europe and Australia (Figure 6, Supplementary Data File S4, available at https://doi.org/10.1016/j.esmoop.2021.100255). The incidence of cervical cancer varied 10-fold with the lowest in North Africa and the Middle East (1.2 per 100 000 people per year) and highest in Southern Latin America (11.7 per 100 000 people per year). The incidence of leukemia varied fourfold to sixfold with the lowest in most parts of Africa and South Asia and highest in Western Europe, high-income Asia Pacific, and East Asia (Figures 2A and 6A, Supplementary Data File S4, available at https://doi.org/10.1016/j.esmoop.2021.100255). The greatest variation was seen in the incidence of cervical cancer, which was higher in high-income North America than in all the other regions. With respect to cancer-associated mortality, the greatest mortality burden for breast cancer was observed in Oceania (5.1 per

Table 3. Worldwide incidence and rates by SDI and regions for the 29 cancer types in 1990 and 2019 among 15-39-year olds and the change in the trends from 1990 to 2019

	1990		2019		1990-2019 EAPC, No. (95% CI)
	Incident cases	Rate per 100 000	Incident cases	Rate per 100 000	
Sex					
Female	479 401	44.22	766 692	52.32	0.37 (0.36 to 0.38)
Male	359 935	32.43	568 407	37.82	0.38 (0.37 to 0.39)
Sociodemographic index					
High SDI	248 945	77.05	304 186	91.81	0.57 (0.56 to 0.58)
High—middle SDI	210 024	43.43	321 162	62.15	0.99 (0.98 to 1.00)
Middle SDI	230 698	30.90	381 888	40.83	0.70 (0.69 to 0.71)
Low—middle SDI	107 196	24.07	217 792	29.61	0.51 (0.50 to 0.53)
Low SDI	42 055	21.69	103 945	23.21	0.18 (0.16 to 0.19)
Region					
Africa					
Central Sub-Saharan Africa	4335	20.88	10 463	20.19	−0.20 (−0.22 to −0.19)
Eastern Sub-Saharan Africa	16 904	24.03	39 376	23.61	−0.21 (−0.22 to −0.20)
Western Sub-Saharan Africa	11 622	16.34	32 628	18.21	0.39 (0.38 to 0.41)
Southern Sub-Saharan Africa	7478	34.10	11 965	35.52	−0.24 (−0.25 to −0.22)
North Africa and Middle East	32 025	23.58	92 962	35.94	1.47 (1.46 to 1.49)
America					
Andean Latin America	4833	31.27	10 928	42.55	0.97 (0.96 to 0.98)
Caribbean	5392	36.35	7864	43.38	0.32 (0.31 to 0.33)
Central Latin America	22 198	32.54	44 804	44.36	1.04 (1.02 to 1.05)
High-income North America	131 451	116.25	161 026	132.52	0.55 (0.54 to 0.56)
Southern Latin America	9272	48.58	15 991	62.87	0.79 (0.78 to 0.80)
Tropical Latin America	23 695	36.84	43 422	48.73	1.00 (0.99 to 1.01)
Asia					
Central Asia	11 886	41.74	16 297	43.01	−0.48 (−0.49 to −0.47)
East Asia	204 664	36.09	318 991	61.85	1.47 (1.46 to 1.48)
High-income Asia Pacific	30 944	45.81	29 060	55.30	0.91 (0.90 to 0.92)
South Asia	91 146	21.10	208 127	27.06	0.69 (0.68 to 0.71)
Southeast Asia	56 624	28.77	98 028	36.09	0.51 (0.50 to 0.52)
Europe					
Central Europe	25 360	55.10	23 641	66.38	0.72 (0.71 to 0.73)
Eastern Europe	44 349	51.69	50 680	73.84	0.98 (0.97 to 0.99)
Western Europe	98 068	68.07	108 039	82.447	0.43 (0.42 to 0.44)
Oceania					
Australasia	6293	77.17	8821	90.78	0.32 (0.31 to 0.33)
Other Oceania countries	788	29.95	1976	36.31	0.59 (0.58 to 0.60)

CI, confidence interval; EAPC, estimated annual percentage change; SDI, sociodemographic index.

100 000 people per year), Southeast Asia (2.5 per 100 000 people per year), and the Caribbean (2.0 per 100 000 people per year). The mortality burden of cervical cancer varied 10-fold, ranging from 0.25 per 100 000 people per year in North Africa and the Middle East to 2.5 per 100 000 people per year in the Caribbean and Southern Sub-Saharan Africa. The five regions with the highest mortality rates for leukemia were Andean Latin America, Central Latin America, East Asia, Central Asia, and other Oceania countries, all with rates of >2.0 per 100 000 people per year (Figures 2B and 6B, Supplementary Data File S4, available at https://doi.org/10.1016/j.esmoop.2021.100255).

DISCUSSION

To the best of our knowledge, this is the first comprehensive analysis of worldwide cancer burden in AYAs in recent years, adding detailed profiles to the limited available epidemiological data of cancers in AYAs. Overall, the global incidence of cancer in AYAs in 2019 was 44.99 per 100 000 people per year, and the corresponding death rate was 13.39 per 100 000 people per year. We reported population-based trends in cancer incidence and mortality, with a focus on the considerable variations in cancer types within this population when stratified by age, sex, SDI, and geographical regions. Our study highlighted the need for tailored cancer control measures in this neglected subpopulation.

The death rate of AYAs with cancers showed a significant decreasing trend from 1990 to 2019, which became more pronounced from 2000. Consistent with established epidemiological data, the reduction of cancer burden in AYAs was mainly from the contributions of the high and high—middle SDI regions,[2,6] suggesting that there were variations in the cancer burden in the different SDI regions within this age groups. Previous studies have shown that cancer survival rates between different income countries varied for reasons such as variations in cancer screening, detection modalities, insurance status, specialized health care availability, treatment used, and the knowledge of cancer prevention.[17-19] These findings indicated that rational allocation of existing

Table 4. Worldwide deaths and rates by SDI and regions for the 29 cancer types among 15-39-year olds in 1990 and 2019 and the change in the trends from 1990 to 2019

	1990		2019		1990-2019 EAPC, No. (95% CI)
	Death cases	Rate	Death cases	Rate per 100 000	
Sex					
Female	176 497	16.28	20 3011	13.85	−0.92 (−0.94 to −0.90)
Male	172 732	15.56	194 571	12.94	−0.95 (−0.97 to −0.93)
Sociodemographic index					
High SDI	46 779	14.47	33 476	10.10	−1.47 (−1.49 to −1.45)
High−middle SDI	90 769	18.77	76 939	14.89	−1.37 (−1.38 to −1.35)
Middle SDI	126 469	16.93	132 396	14.15	−1.02 (−1.04 to −1.01)
Low−middle SDI	61 075	13.71	100 905	13.72	−0.20 (−0.22 to −0.18)
Low SDI	23 960	12.36	53 608	11.97	−0.16 (−0.18 to −0.14)
Region					
Africa					
Central Sub-Saharan Africa	2395	11.53	5382	10.39	−0.45 (−0.47 to −0.43)
Eastern Sub-Saharan Africa	9307	13.20	20 041	12.01	−0.44 (−0.46 to −0.42)
Western Sub-Saharan Africa	6379	8.97	16 443	9.17	0.07 (0.05 to 0.09)
Southern Sub-Saharan Africa	3613	16.47	5059	15.02	−0.65 (−0.66 to −0.63)
North Africa and Middle East	16 692	12.29	30 084	11.63	−0.28 (−0.30 to −0.26)
America					
Andean Latin America	2449	15.85	3811	14.84	−0.32 (−0.31 to −0.34)
Caribbean	2254	15.19	2865	15.80	−0.03 (−0.05 to −0.01)
Central Latin America	9453	13.85	13 971	13.83	−0.03 (−0.05 to −0.01)
High-income North America	16 326	14.43	11 830	9.73	−1.56 (−1.57 to −1.54)
Southern Latin America	3534	18.51	3876	15.24	−0.79 (−0.81 to −0.77)
Tropical Latin America	9157	14.23	12 468	13.99	−0.04 (−0.06 to −0.02)
Asia					
Central Asia	5665	19.89	6563	17.32	−1.16 (−1.18 to −1.15)
East Asia	118 957	20.98	85 630	16.60	−1.50 (−1.52 to −1.49)
High-income Asia Pacific	9900	14.65	4441	8.45	−1.96 (−1.98 to −1.94)
South Asia	52 871	12.23	100 793	13.10	0.07 (0.05 to 0.09)
Southeast Asia	30 603	15.54	40 558	14.93	−0.40 (−0.42 to −0.39)
Europe					
Central Europe	9542	20.73	5183	14.55	−1.36 (−1.37 to −1.34)
Eastern Europe	17 513	20.41	13 303	19.38	−0.92 (−0.93 to −0.90)
Western Europe	21 064	14.62	13 262	10.12	−1.56 (−1.58 to −1.54)
Oceania					
Australasia	1116	13.69	1005	10.34	−1.2 (−1.22 to −1.18)
Other Oceania countries	429	16.30	1002	18.41	0.41 (0.39 to 0.43)

CI, confidence interval; EAPC, estimated annual percentage change; SDI, sociodemographic index.

or given resources is required to reduce the burden of cancer in AYAs in developing countries.

Female predominance is a peculiarity of the cancer burden in AYAs. Cervical and breast cancers were the most common cancer types in AYAs in most countries. These sex-based characteristics of cancer burden should be considered as important aspects when designing cancer control measures for AYAs. For example, the leading reason for adverse outcomes in AYAs with breast cancers is that they are more likely to have familial cancer predisposition genes than older women are, and in addition, a substantial proportion of them are found to have distant metastases at the time of diagnosis.[3,20,21] Enhanced screening for predisposing genes may be an important measure in the early diagnosis of breast cancer and may, thus, reduce the cancer burden in AYAs. The incidence rate of cervical cancer in the low SDI regions was five times higher than that in the high SDI regions. The difficulty in reducing cervical cancer risk is associated with an elevated transmission of human papillomavirus (HPV) in the increasing young urban population in developing countries.[3,22] Therefore a national HPV vaccination program of HPV-naïve people may have a significant effect in curbing the incidence trends.

AYA cancers in the low SDI regions were more likely to be associated with chronic infections, including infections with HPV, hepatitis B/C virus, *Helicobacter pylori*, Epstein−Barr virus, and human herpesvirus 8, than were the cases in the high SDI region. The analysis of the GLOBOCAN 2012 data showed that 30% of all cancers were linked to chronic infections in the low SDI countries compared with 10% in the very high SDI countries.[6] Our data showed that the burden of cervical cancer was ranked first in both low and middle−low SDI regions; however, the burden of other infection-associated cancers such as lymphomas and liver cancer decreased significantly. These results emphasize the effectiveness of the cancer control measures of the past decade while providing a direction for future strategies to reduce the cancer burden in AYAs.

It should be noted that the implications of the cancer burden in AYAs are beyond the number of incident cases and deaths. Survivors of AYA cancers often live for a long

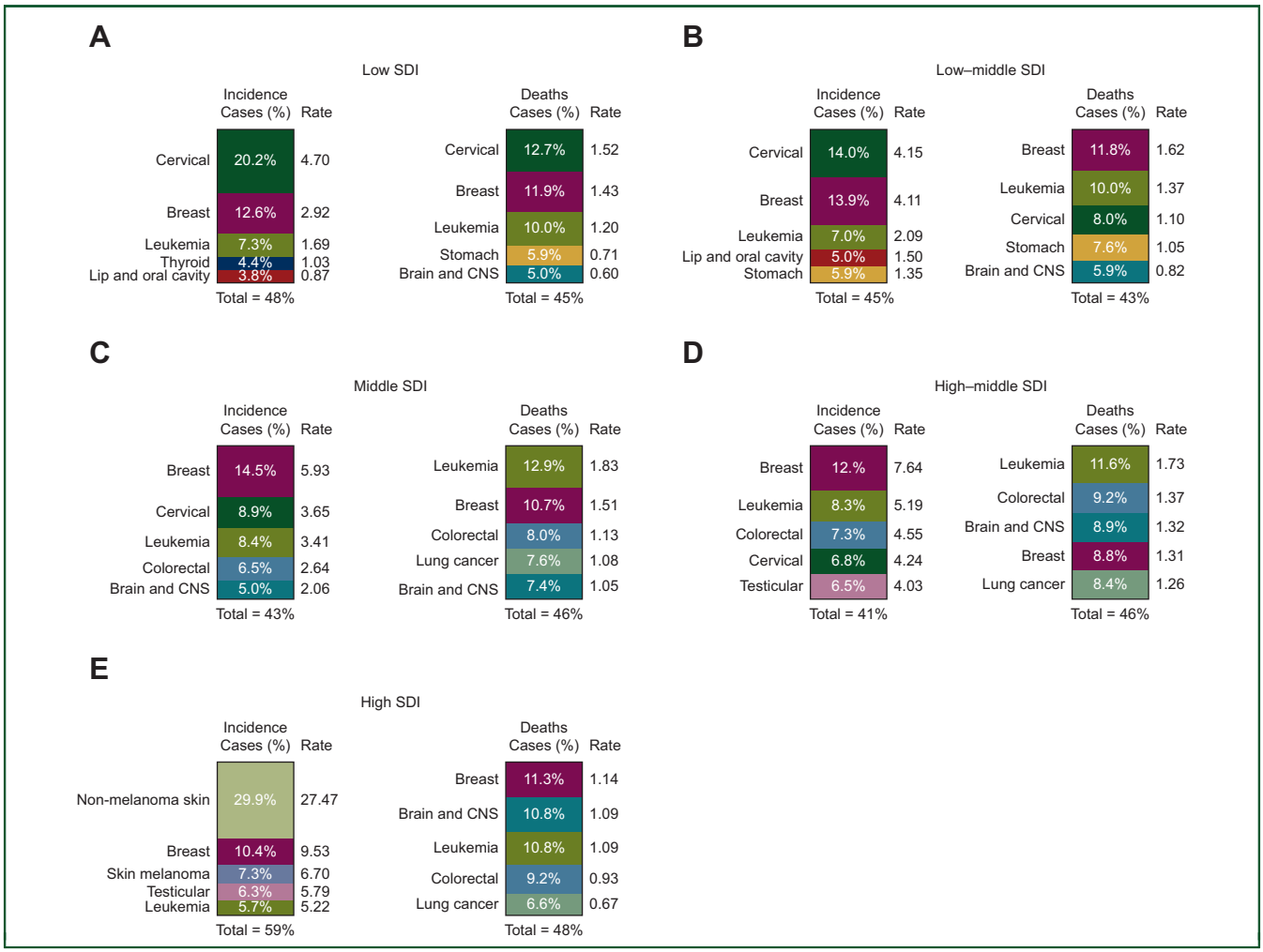

Figure 4. Worldwide distribution of the top five cancer types by SDI quintile in terms of incidence and death cases among 15-39-year olds in 2019.
(A) Low SDI; (B) low–middle SDI; (C) middle SDI; (D) high–middle SDI; (E) high SDI.
CNS, central nervous system; SDI, sociodemographic index.

time after their diagnosis, resulting in an increased risk of the development of cancer- and treatment-related 'late effects,' including secondary malignancies,[8,23,24] cardiovascular diseases,[25,26] endocrine dysfunctions,[27] neurocognitive impairments,[9,28] exercise dysfunctions, and psychological distress.[29] Consequently, the cancer burden in AYAs is characterized mainly by the proportion of quality of life lost at an individual level. It also results in considerable losses to society in terms of social structure. In addition, despite a decline in productivity, AYA cancer survivors generally have higher annual medical expenditures than adults without a history of cancer.[30,31] In particular, this situation is worse in the low SDI regions, where most patients paid out-of-pocket for both the diagnosis and treatment owing to the paucity of health insurance. Therefore, in addition to specific medical measures such as effective prevention, timely diagnoses, and high-quality care, some early screening programs with a limited cost for AYAs might have a significant effect, particularly those targeting cervical cancer and breast cancer. Besides, collaborative work taking into account economic, social, and psychological aspects should be tailored to reduce the cancer burden among this specific age group.

The limitations of the GBD data in accessing cancer incidence and mortality have been described extensively elsewhere.[15,32] Briefly, the accuracy of the results depended on the quality and availability of the GBD data at a given time. Furthermore, the classification of cancer in the GBD was not identical to the recommended classification for cancers in AYAs.[33] Moreover, the GBD Study was based on countries and regions, resulting in a lack of analysis on the influence of race. Finally, the cancer incidence rate may have been influenced by the evolution of cancer diagnostic technology and criteria.

Conclusion

In summary, this study provided comprehensive estimates of the worldwide cancer burden among AYAs. Our results

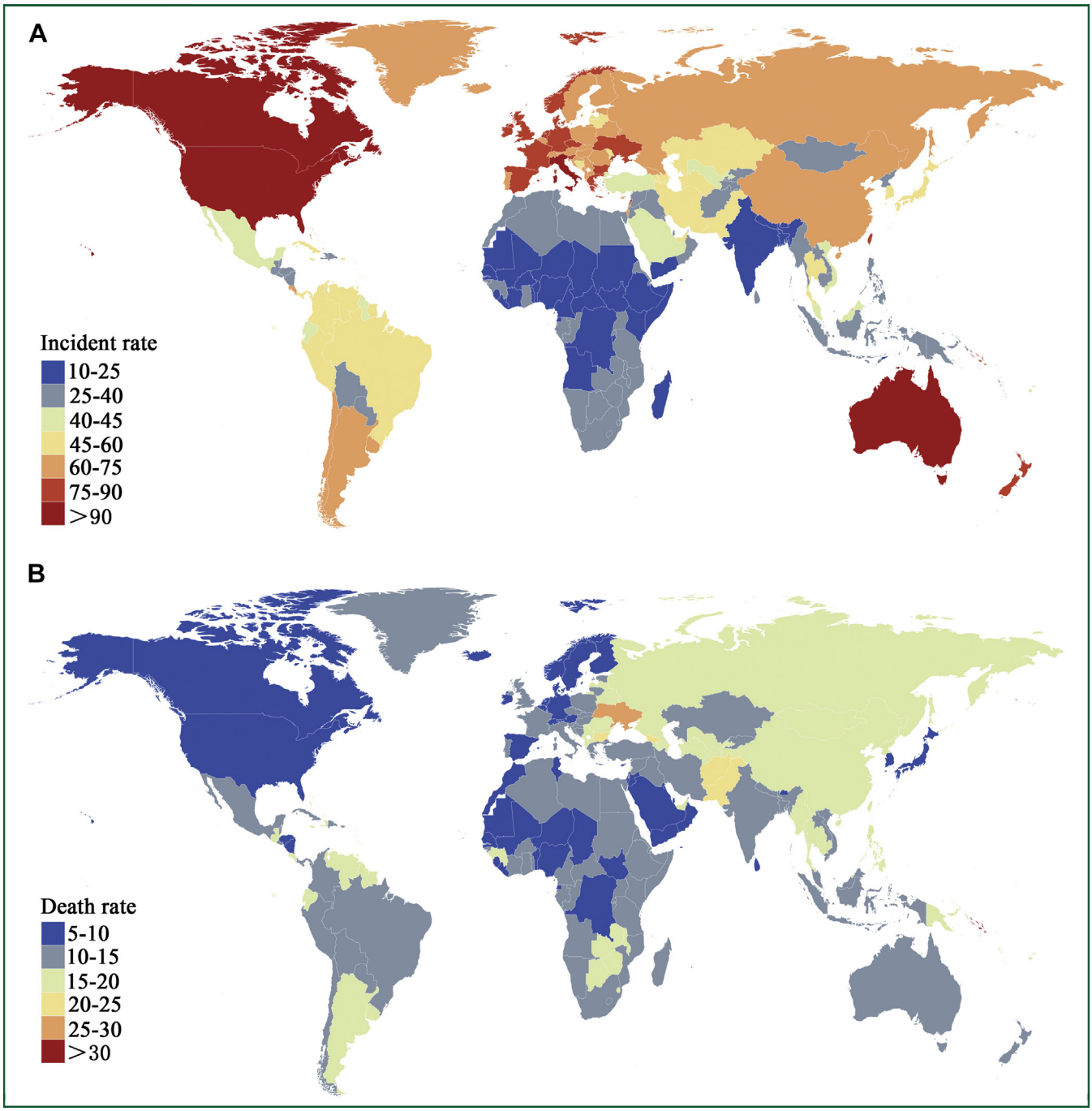

Figure 5. **Global map of (A) incidence and (B) death rate for total cancers by country among 15-39-year olds in 2019.**

show that the global cancer burden among AYAs is distinct from that in younger or older age groups and varies significantly by sex, age, SDI, and GBD regions. Although there has been rapid progress in the treatment and improvement in the prognosis of cancer over the last decade, the cancer burden in the AYA population is considerable in the low SDI regions. These findings provide a direction for the rational allocation of limited resources and the formulation of policies.

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Not applicable.

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DISCLOSURE

The authors declare that they have no competing interests.

DATA SHARING

The datasets and material used and/or analyzed during this study are available from the Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-results-tool).

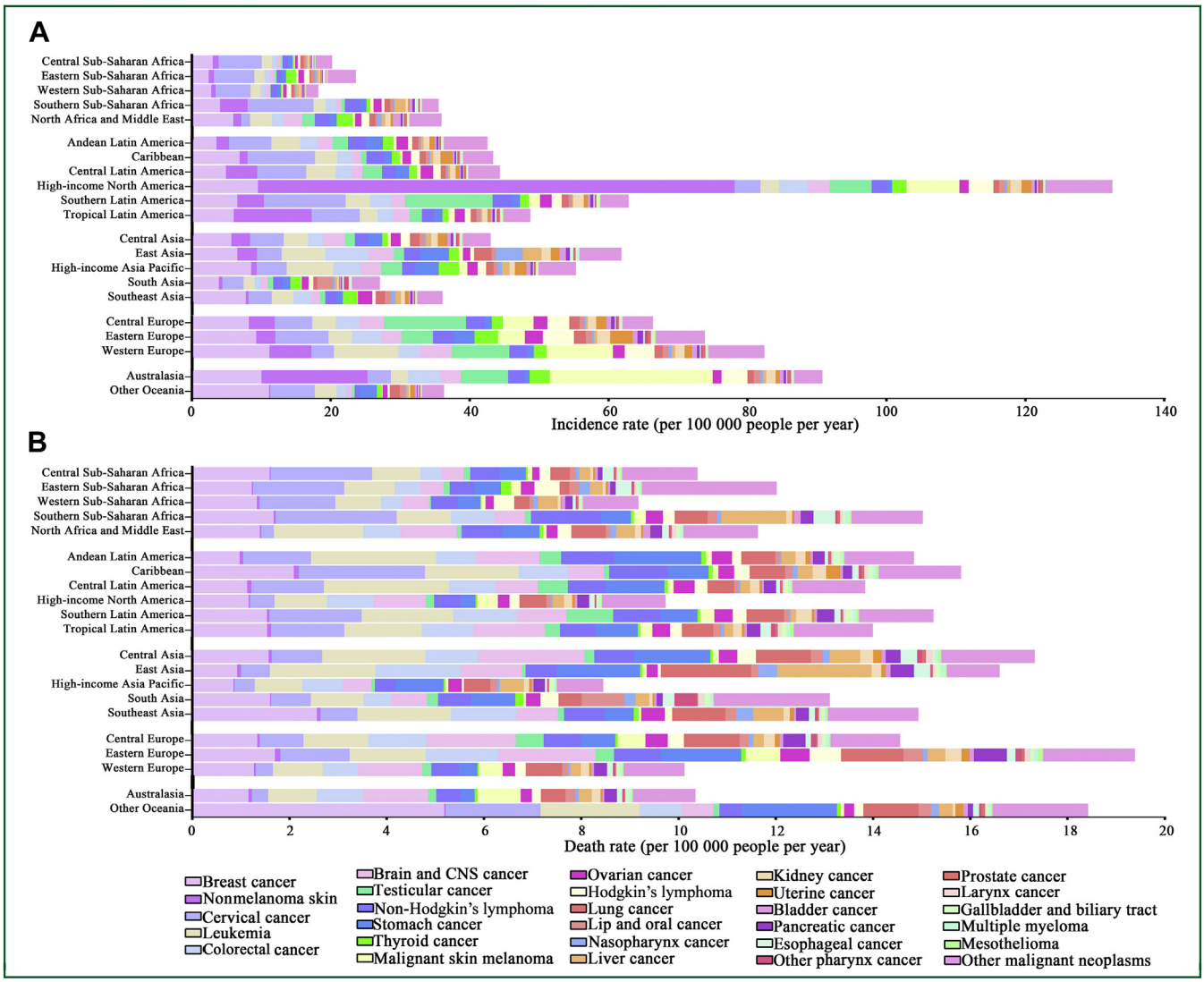

Figure 6. Incidence and death rates for the 29 cancer types by geographical region among 15-39-year olds in 2019.
(A) Incidence rates; (B) death rates.
CNS, central nervous system.

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