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Global disease burden and trends of leukemia attributable to occupational risk from 1990 to 2019: An observational trend study

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Background: Leukemia caused by occupational risk is a problem that needs more attention and remains to be solved urgently, especially for acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), and chronic lymphoid leukemia (CLL). However, there is a paucity of literature on this issue. We aimed to assess the global burden and trends of leukemia attributable to occupational risk from 1990 to 2019.

Methods: This observational trend study was based on the Global Burden of Disease (GBD) 2019 database, the global deaths, and disability-adjusted life years (DALYs), which were calculated to quantify the changing trend of leukemia attributable to occupational risk, were analyzed by age, year, geographical location, and socio-demographic index (SDI), and the corresponding estimated annual percentage change (EAPC) values were calculated.

Results: Global age-standardized DALYs and death rates of leukemia attributable to occupational risk presented significantly decline trends with EAPC [−0.38% (95% CI: −0.58 to −0.18%) for DALYs and −0.30% (95% CI: −0.45 to −0.146%) for death]. However, it was significantly increased in people aged 65−69 years [0.42% (95% CI: 0.30−0.55%) for DALYs and 0.38% (95% CI: 0.26−0.51%) for death]. At the same time, the age-standardized DALYs and death rates of ALL, AML, and CLL were presented a significantly increased trend with EAPCs [0.78% (95% CI: 0.65−0.91%), 0.87% (95% CI: 0.81−0.93%), and 0.66% (95% CI: 0.51−0.81%) for DALYs, respectively, and 0.75% (95% CI: 0.68−0.82%), 0.96% (95% CI: 0.91−1.01%), and 0.55% (95% CI: 0.43−0.68%) for death], respectively. The ALL, AML, and CLL were shown an upward trend in almost all age groups.

Conclusion: We observed a substantial reduction in leukemia due to occupational risks between 1990 and 2019. However, the people aged 65–69 years and burdens of ALL, AML, and CLL had a significantly increased trend in almost all age groups. Thus, there remains an urgent need to accelerate efforts to reduce leukemia attributable to occupational risk-related death burden in this population and specific causes.

KEYWORDS

leukemia, AML, ALL, global burden disease, death rate

Introduction

Cancer has the highest mortality rate among all human diseases (1). The World Health Organization (WHO) classifies tumors based on evidence that tumors occur in various organ systems. It is the global standard for diagnosis, research, cancer registration, and public health monitoring (2). Some kinds of cancer grow rapidly, while others grow slowly. Most kinds of leukemia progress quickly. Hematological tumors can be divided into three different categories, namely, leukemia, lymphoma, and myeloma (3). Among them, leukemia can be further divided into acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL), chronic myeloid leukemia (CML), and other leukemia (4). In this study, we found that AML and ALL had higher DALY rates and death rates compared with other kinds.

Acute myeloid leukemia is the most common in elderly patients, but the incidence rate in young people is also increasing every year (5), with an incidence of over 20,000 cases per year in the United States alone (6). It has been estimated that ∼21,450 adults (11,650 men and 9,800 women) will be diagnosed with AML in 2019 (7). Of all subtypes of leukemia, AML has the highest mortality rate (62%) (7). The excessive accumulation of immature hematopoietic cells in blood and bone marrow, gene mutations, genetics, and other factors will lead to the occurrence of tumors (8). ALL is the most common subtype of childhood leukemia. ALL have a high mortality rate due to excessive accumulation of immature lymphocytes in the peripheral blood and bone marrow (9, 10).

Occupational exposure has been related to higher risks of several kinds of cancer (11, 12). It has brought tremendous health and economic burden for people all over the world (13). However, insufficient attention has been paid to the detection, diagnosis, and monitoring of occupational exposure and its associated diseases, especially leukemia. It is well-accepted that occupational exposure to formaldehyde and benzene causes leukemia (14, 15). The researchers compared occupational exposure to formaldehyde with the risk of leukemia in community-based case-control studies. The proportion of leukemia in occupationally exposed cohorts will increase significantly (16). In 2009, the International Agency for Research on Cancer (IARC) regarded formaldehyde as a risk factor for leukemia (17, 18). Researchers often focus on the relationship between formaldehyde and general lymphohematopoietic cancer or leukemia, but the issue of occupational exposure has not attracted their attention (16, 19, 20).

The Global Burden of Disease (GBD) study was originally authorized by the World Bank and added to the landmark World Development Report 1993 (21). Since 1990, GBD has made the most comprehensive efforts to systematically monitor and master the world's health problems (22). We used the GBD database to analyze leukemia attributable to occupational risk incidences and deaths in the general population by sex, social development index (SDI), and reason for the 1990–2019 period at regional and global levels. We aimed to provide valuable insights into data-based healthcare regimens and provide a better understanding of the global burden of leukemia attributable to occupational risk as an important complement to previous GBD studies.

Methods

Data sources

Data on the burden of leukemia attributable to occupational risk were downloaded from the Global Health Data Exchange GBD Results Tool (http://ghdx.healthdata.org/gbd-results-tool), including death rates and disability-adjusted life years (DALYs). GBD values were reported as estimated values with 95% uncertainty intervals (UIs), and a posterior distribution was used to calculate the 25th and 975th ranked estimates from random 1,000 draws (23). Information such as the socio-demographic index (SDI) and corresponding age-standardized rates was also downloaded from this website for the following correlation analysis. Based on the SDI, 204 countries and territories were divided into five super regions, namely, low, low-middle, middle, middle, and high SDI (24, 25). According to GBD 2019, SDI is an indicator of a country's level of health

TABLE 1 The number and age-standardized rate of DALYs and death of leukemia attributable to occupational risk in 1990 and 2019.

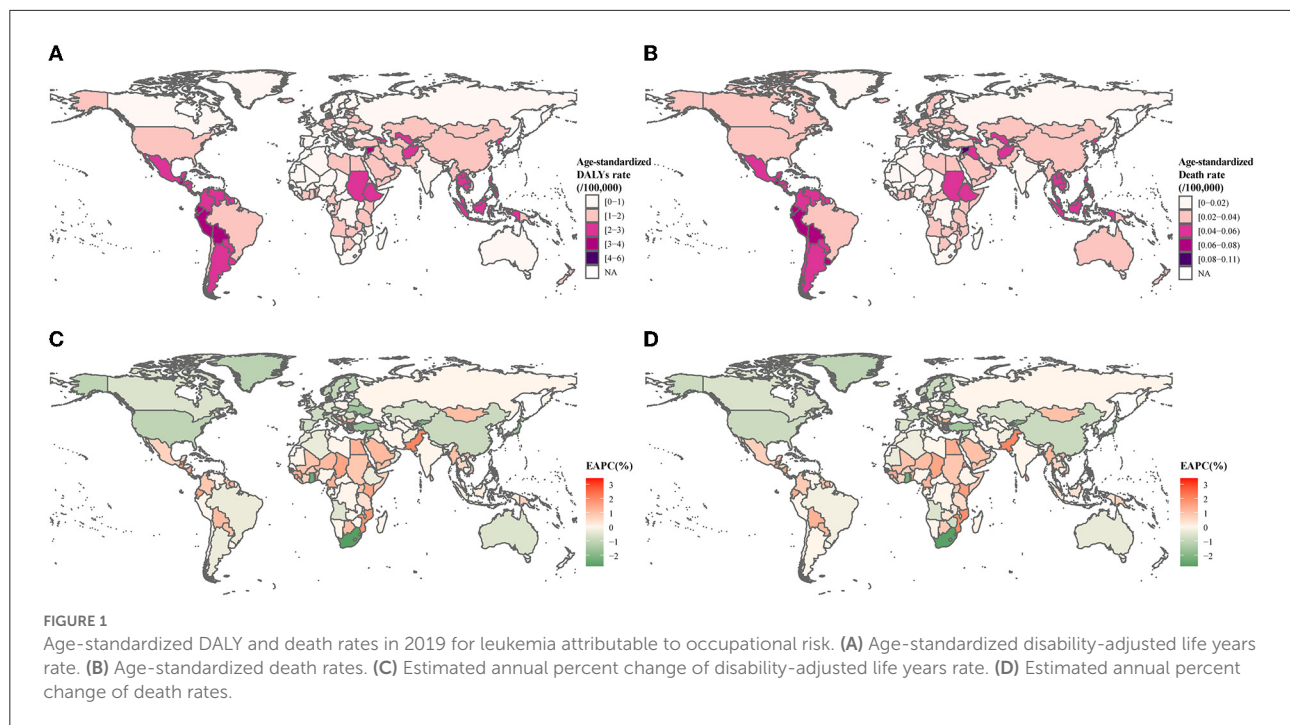|	DALYS (95% UI)					Deaths (95% UI)				
	1990		2019		EAPC (95% CI)	1990		2019		EAPC (95% CI)
	Number	Age-Standardized rate	Number	Age-Standardized rate		Number	Age-Standardized rate	Number	Age-Standardized rate	
Global	80,359 (39,266–118,130)	1.5609 (0.7676–2.2942)	113,715 (54,505–167,831)	1.3986 (0.669–2.0648)	−0.38% (95% CI: −0.58 to −0.18%)*	1,612 (792–2,369)	0.0326 (0.0161–0.0481)	2,455 (1,181–3,645)	0.0299 (0.0144–0.0445)	−0.3% (95% CI: −0.45 to −0.14%)*
Gender										
Male	46,410 (22,691–68,190)	1.7925 (0.8719–2.6295)	66,189 (32,299–98550)	1.6267 (0.7944–2.4214)	−0.33% (−0.41 to −0.24%)*	932 (460–1,370)	0.0378 (0.0186–0.0557)	1,425 (699–2,131)	0.035 (0.0172–0.0524)	−0.33% (−0.53 to −0.14%)*
Female	33,949 (17,064–51,519)	1.3279 (0.6663–2.011)	47,526 (21,915–71,940)	1.1703 (0.5417–1.7683)	−0.44% (−0.69 to −3.33%)*	680 (340–1,032)	0.0275 (0.0137–0.0416)	1,030 (478–1,563)	0.025 (0.0116–0.0379)	−0.27% (−0.30 to −0.23%)*
Age group										
15–49 year	69,226 (34,198–101,973)	2.5524 (1.2609–3.7598)	90,522 (42,924–133,843)	2.3004 (1.0908–3.4013)	−0.36% (−0.58 to −0.13%)*	1,229 (607–1,808)	0.0453 (0.0224–0.0667)	1,635 (783–2,420)	0.0416 (0.0199–0.0615)	−0.3% (−0.51 to −0.09%)*
50–69 year	9,616 (4,607–14,350)	1.4097 (0.6754–2.1037)	18,828 (8,926–28,358)	1.3654 (0.6473–2.0565)	−0.11% (−0.16 to −0.06%)*	302 (144–451)	0.0442 (0.0211–0.0661)	589 (280–887)	0.0427 (0.0203–0.0643)	−0.11% (−0.19 to −0.04%)*
70+ year	1,517 (608–2,360)	0.7528 (0.3015–1.1712)	4,365 (1,892–6,819)	0.9413 (0.408–1.4706)	0.79% (0.69–0.88%)*	81 (33–126)	0.0402 (0.0162–0.0624)	230 (101–358)	0.0497 (0.0218–0.0773)	0.74% (0.64–0.84%)*
SDI region										
High SDI	12,245 (3,626–20,127)	1.3381 (0.3967–2.1986)	13,025 (4,307–21,114)	1.0821 (0.3572–1.7444)	−0.71% (−0.82 to −0.61%)*	282 (83–463)	0.03 (0.0088–0.0493)	343 (108–558)	0.0251 (0.0082–0.0408)	−0.6% (−0.64 to −0.55%)*
High-Middle SDI	21,953 (11,034–32,036)	1.8066 (0.9141–2.6395)	25,292 (12,559–37,288)	1.5348 (0.7621–2.2598)	−0.55% (−0.81 to −0.28%)*	442 (223–646)	0.037 (0.0187–0.0541)	552 (272–817)	0.0318 (0.0158–0.0473)	−0.51% (−0.74 to −0.28%)*
Middle SDI	30,894 (14,963–45,905)	1.8519 (0.8966–2.7548)	44,229 (20,790–65,558)	1.6778 (0.7894–2.4881)	−0.34% (−0.59 to −0.09%)*	590 (286–876)	0.0375 (0.0182–0.0557)	925 (435–1383)	0.0348 (0.0164–0.052)	−0.22% (−0.4 to −0.03%)*
Low-Middle SDI	11,144 (5,399–16,808)	1.1395 (0.5449–1.7147)	20,970 (9,883–31,866)	1.1817 (0.5556–1.7971)	0.13% (−0.05–0.31%)	216 (103–325)	0.0235 (0.0113–0.0353)	432 (202–659)	0.0252 (0.0119–0.0385)	0.24% (0.09–0.38%)*
Low SDI	4,081 (1,876–6,554)	1.019 (0.4688–1.6285)	10,119 (4,754–15,494)	1.1048 (0.5093–1.6935)	0.28% (0.2–0.37%)*	81 (37–130)	0.0219 (0.0102–0.0351)	201 (93–309)	0.0241 (0.011–0.0372)	0.33% (0.24–0.42%)*

(Continued)

TABLE 1 (Continued)

	DALYS (95% UI)				DALYS EAPC (95% CI)	Deaths (95% UI)				Deaths EAPC (95% CI)
	1990		2019			1990		2019		
	Number	Age-Standardized rate	Number	Age-Standardized rate		Number	Age-Standardized rate	Number	Age-Standardized rate	
Type of cause										
Acute lymphoid leukemia	12,017	0.223	22,397	0.2788	0.78%	218	0.0042	419	0.0052	0.75%
	(5,800–18,336)	(0.1069–0.34)	(10,592–33,563)	(0.1318–0.418)	(0.65–0.91%)*	(105–334)	(0.002–0.0064)	(198–633)	(0.0025–0.0078)	(0.68–0.82%)*
Acute myeloid leukemia	15,418	0.3035	31,670	0.3891	0.87%	321	0.0066	712	0.0087	0.96%
	(7,407–23,786)	(0.1446–0.468)	(15,108–47,562)	(0.185–0.5846)	(0.81–0.93%)*	(152–498)	(0.0031–0.0103)	(346–1080)	(0.0042–0.0131)	(0.91–1.01%)*
Chronic lymphoid leukemia	2,637	0.0572	5,710	0.0687	0.66%	70	0.0016	155	0.0019	0.55%
	(1,247–4,046)	(0.0269–0.0877)	(2,703–8,702)	(0.0324–0.1047)	(0.51–0.81%)*	(32–108)	(0.0007–0.0025)	(74–237)	(0.0009–0.0028)	(0.43–0.68%)*
Chronic myeloid leukemia	10,354	0.2065	13,455	0.1652	−0.74%	216	0.0045	285	0.0035	−0.86%
	(4,989–15,725)	(0.0996–0.3129)	(6,353–20,693)	(0.078–0.2542)	(−0.89 to −0.6%)*	(105–327)	(0.0022–0.0068)	(132–438)	(0.0016–0.0053)	(−1.03 to −0.69%)*
Other leukemia	39,933	0.7709	40,483	0.4969	−1.51%	787	0.0158	884	0.0108	−1.33%
	(19,388–60,206)	(0.3764–1.1628)	(19,388–59,947)	(0.2374–0.736)	(−1.7 to −1.32%)*	(380–1182)	(0.0076–0.0236)	(425–1316)	(0.0052–0.016)	(−1.48 to −1.19%)*
Southeast Asia, east Asia, and Oceania										
Southeast Asia	8,013	1.8404	14,872	2.0371	0.36%	153	0.0377	310	0.043	0.47%
	(3,908–12,237)	(0.8829–2.8079)	(6,972–22,458)	(0.9542–3.0779)	(0.14–0.58%)*	(74–233)	(0.0183–0.0573)	(146–470)	(0.0202–0.0652)	(0.31–0.63%)*
East Asia	28,451	2.1654	29,187	1.7044	−0.83%	543	0.0432	616	0.034	−0.84%
	(14,364–42,465)	(1.0907–3.2396)	(14,636–44,374)	(0.8521–2.5867)	(−1.33 to −0.34%)*	(271–809)	(0.0218–0.0644)	(312–934)	(0.017–0.0514)	(−1.23 to −0.44%)*
Oceania	84	1.4493	206	1.6147	0.39%	2	0.0292	4	0.033	0.43%
	(38–136)	(0.6591–2.3427)	(86–365)	(0.672–2.8499)	(0.31–0.47%)*	(1–3)	(0.0131–0.0473)	(2–7)	(0.0137–0.0575)	(0.36–0.51%)*
Sub-Saharan Africa										
Western Sub-Saharan Africa	1,301	0.8805	3,323	0.9098	0.11%	26	0.0187	65	0.0195	0.14%
	(630–1,983)	(0.4208–1.3465)	(1,452–5,392)	(0.3995–1.4641)	(−0.01–0.24%)	(12–39)	(0.0089–0.0287)	(28–104)	(0.0085–0.031)	(0–0.27%)*
Central Sub-Saharan Africa	456	1.0641	1,122	1.0326	−0.09%	9	0.0223	21	0.0216	−0.1%
	(213–725)	(0.5–1.7038)	(520–1,850)	(0.4854–1.7219)	(−0.31–0.13%)	(4–14)	(0.0104–0.0353)	(10–36)	(0.01–0.0358)	(−0.31–0.11%)
Southern Sub-Saharan Africa	693	1.5077	698	0.8289	−2.14%	13	0.0309	13	0.0165	−2.11%
	(316–1,063)	(0.6848–2.3022)	(304–1,109)	(0.3623–1.2965)	(−2.61 to −1.67%)*	(6–20)	(0.0143–0.047)	(6–21)	(0.0072–0.0256)	(−2.6 to −1.63%)*
Eastern Sub-Saharan Africa	1,892	1.3829	4,615	1.4389	0.14%	37	0.03	92	0.0323	0.26%
	(836–3,251)	(0.6181–2.3596)	(2,009–7,528)	(0.621–2.3458)	(0–0.27%)*	(17–64)	(0.0137–0.0508)	(40–150)	(0.0139–0.0531)	(0.11–0.41%)*

(Continued)

TABLE 1 (Continued)

	DALYS (95% UI)					Deaths (95% UI)				
	1990		2019		EAPC (95% CI)	1990		2019		EAPC (95% CI)
	Number	Age-Standardized rate	Number	Age-Standardized rate		Number	Age-Standardized rate	Number	Age-Standardized rate	
South Asia	7,959	0.8339	16,167	0.8775	0.17%	158	0.0176	337	0.019	0.25%
	(3,829–11,931)	(0.4039–1.2503)	(7,637–25,073)	(0.415–1.3532)	(−0.11–0.45%)	(76–237)	(0.0085–0.0266)	(157–518)	(0.0089–0.0292)	(−0.01–0.51%)
Latin America and Caribbean										
Tropical Latin America	2,759	1.9048	4,344	1.76	−0.26%	54	0.0397	94	0.0378	−0.15%
	(1,283–4,032)	(0.8934–2.7924)	(1,981–6544)	(0.8031–2.6522)	(−0.39 to −0.13%)*	(25–79)	(0.0187–0.0583)	(42–142)	(0.0171–0.0572)	(−0.27 to −0.03%)*
Caribbean	548	1.616	990	2.0017	0.76%	11	0.0342	22	0.0431	0.82%
	(262–816)	(0.767–2.4065)	(449–1,511)	(0.907–3.0462)	(0.61–0.91%)*	(5–16)	(0.0164–0.051)	(10–33)	(0.0196–0.0657)	(0.68–0.96%)*
Andean Latin America	863	2.5525	2,123	3.2553	0.81%	17	0.0528	43	0.0683	0.86%
	(405–1,355)	(1.1909–3.9913)	(939–3,345)	(1.4393–5.1235)	(0.11–1.51%)*	(8–26)	(0.0248–0.0825)	(19–69)	(0.0307–0.1079)	(0.19–1.54%)*
Central Latin America	3,386	2.2682	7,057	2.6878	0.61%	63	0.0457	142	0.0548	0.64%
	(1,654–4,978)	(1.1108–3.3323)	(3,264–10,531)	(1.2418–4.0114)	(0.33–0.89%)*	(31–93)	(0.0225–0.0672)	(66–214)	(0.0255–0.0825)	(0.38–0.89%)*
North Africa and Middle East	4,688	1.6619	10,081	1.5789	−0.17%	94	0.0359	210	0.0346	−0.13%
	(2,220–7,329)	(0.7832–2.5851)	(4,560–15,281)	(0.71–2.3953)	(−0.27 to −0.07%)*	(44–145)	(0.0169–0.0555)	(94–318)	(0.0154–0.0525)	(−0.21 to −0.04%)*
Central Europe, eastern Europe, and central Asia										
Central Europe	1,275	0.9737	1,252	0.9031	−0.27%	29	0.0213	33	0.0211	−0.04%
	(374–2,116)	(0.2878–1.6158)	(332–2,154)	(0.2423–1.5514)	(−0.44 to −0.11%)*	(8–48)	(0.0062–0.0353)	(9–58)	(0.0056–0.0365)	(−0.19–0.12%)
Central Asia	1,443	2.1779	1,936	1.9269	−0.41%	27	0.0432	38	0.0388	−0.35%
	(653–2,159)	(0.9832–3.2557)	(834–2,968)	(0.8316–2.958)	(−0.65 to −0.17%)*	(12–41)	(0.0195–0.0646)	(16–59)	(0.0168–0.0597)	(−0.61 to −0.09%)*
Eastern Europe	3,077	1.257	2,297	0.965	−0.83%	66	0.0263	53	0.0205	−0.77%
	(830–5,227)	(0.3367–2.1329)	(593–3,982)	(0.2501–1.6661)	(−1.54 to −0.12%)*	(18–113)	(0.007–0.0447)	(13–93)	(0.0053–0.0359)	(−1.24 to −0.29%)*
High-income regions										
High-Income North America	4,526	1.4366	4,584	1.0589	−1.03%	108	0.0336	127	0.0261	−0.83%
	(1,240–7,650)	(0.3921–2.4279)	(1,182–7,868)	(0.2726–1.8226)	(−1.29 to −0.76%)*	(29–182)	(0.0091–0.0566)	(33–219)	(0.0067–0.0448)	(−0.95 to −0.7%)*
High-Income Asia Pacific	2,576	1.3413	1,868	0.8374	−1.65%	56	0.0284	50	0.0186	−1.45%
	(742–4,313)	(0.3881–2.2398)	(509–3,158)	(0.2295–1.4079)	(−1.88 to −1.42%)*	(16–94)	(0.0081–0.0476)	(13–85)	(0.005–0.0315)	(−1.63 to −1.28%)*
Australasia	220	0.9914	301	0.8674	−0.43%	5	0.0232	8	0.0215	−0.24%
	(63–370)	(0.2819–1.6638)	(78–513)	(0.2243–1.4794)	(−0.6 to −0.26%)*	(1–9)	(0.0066–0.0392)	(2–14)	(0.0056–0.0369)	(−0.4 to −0.07%)*
Western Europe	4,925	1.1406	4,950	0.9437	−0.68%	116	0.0254	136	0.022	−0.52%
	(1,365–8,254)	(0.3169–1.9094)	(1,282–8,350)	(0.2439–1.5911)	(−0.85 to −0.51%)*	(32–196)	(0.007–0.0427)	(35–232)	(0.0056–0.0375)	(−0.64 to −0.4%)*
Southern Latin America	1,225	2.5276	1,743	2.4186	−0.17%	26	0.0541	39	0.0526	−0.12%
	(587–1,797)	(1.2148–3.7119)	(787–2,590)	(1.0947–3.5928)	(−0.29 to −0.06%)*	(13–38)	(0.0261–0.0795)	(18–58)	(0.0236–0.0783)	(−0.22 to −0.01%)*

The asterisks represent statistically significant.

FIGURE 1
Age-standardized DALY and death rates in 2019 for leukemia attributable to occupational risk. **(A)** Age-standardized disability-adjusted life years rate. **(B)** Age-standardized death rates. **(C)** Estimated annual percent change of disability-adjusted life years rate. **(D)** Estimated annual percent change of death rates.

development, based on fertility rates for women under 25 and total fertility rates for men, education attainment among those 15 years of age and older, and 10-year lag-distributed average individual incomes (26).

The SDI values range between 0 and 1, which reflect the degree of social development. Our research is compliant with the Guidelines for Accurate and Transparent Health Estimates Reporting.

Definitions

The occupational risk was defined as patients' long-term exposure to carcinogenic factors in the working environment. These kinds of occupational carcinogenic factors include chemical, physical, and biological (27). The DALYs by age, sex, year, and region were collected from GBD 2019. The DALYs is a summary measure that quantifies the overall burden of disease (28, 29).

Statistical analysis

We estimated the number of deaths or DALYs, age-standardized rate DALYs, and deaths to quantify leukemia attributable to occupational risk by age, year, and region.
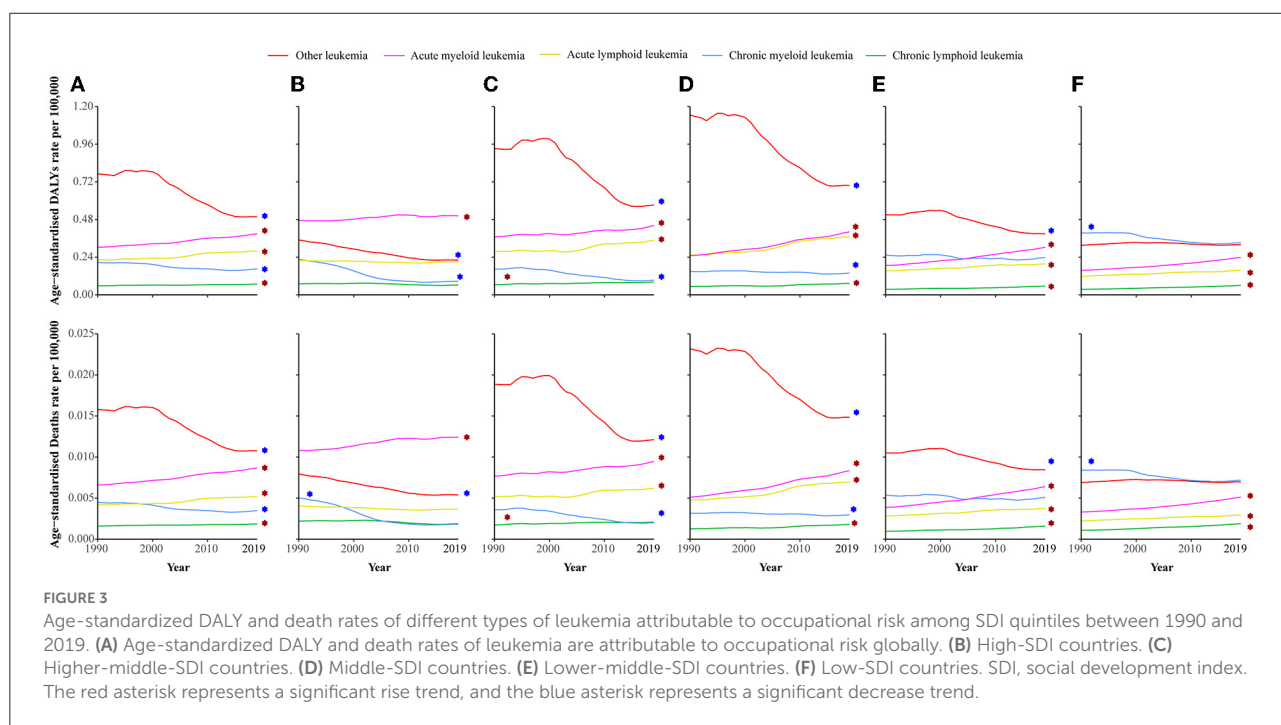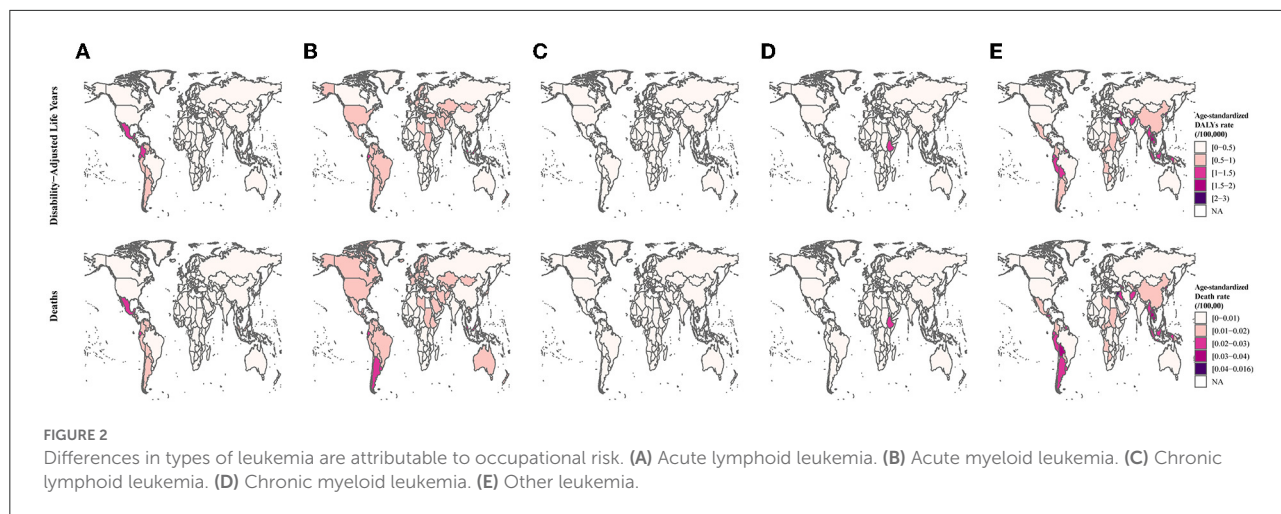
The estimated annual percentage change (EAPC) was calculated to quantify the trends of burdens of leukemia attributable to occupational risk from 1990 to 2019. The regression model was used to fit the age-standardized rate (ASR), that is, $\ln(\text{ASR}) = \alpha + \beta X + \varepsilon$, where y stands for the burden rate and x for the calendar year. EAPC was calculated by $100 \times [\exp(\beta) - 1]$, and its 95% confidence interval (CI) could also be calculated from the model (24, 25, 30). With the EAPC value and its 95% CI above zero, the corresponding age-standardized rate (ASR) was in an upward trend and *vice versa* (31). Moreover, to gain a better understanding of the relationship between the EAPC of ASR and possible facts, a local weighted scatter plot smoothing regression was used to display more detailed information (24, 25). All statistical analyses were done using R (version 3.6.0).

Results

The distribution and its change trend of leukemia attributable to occupational risk
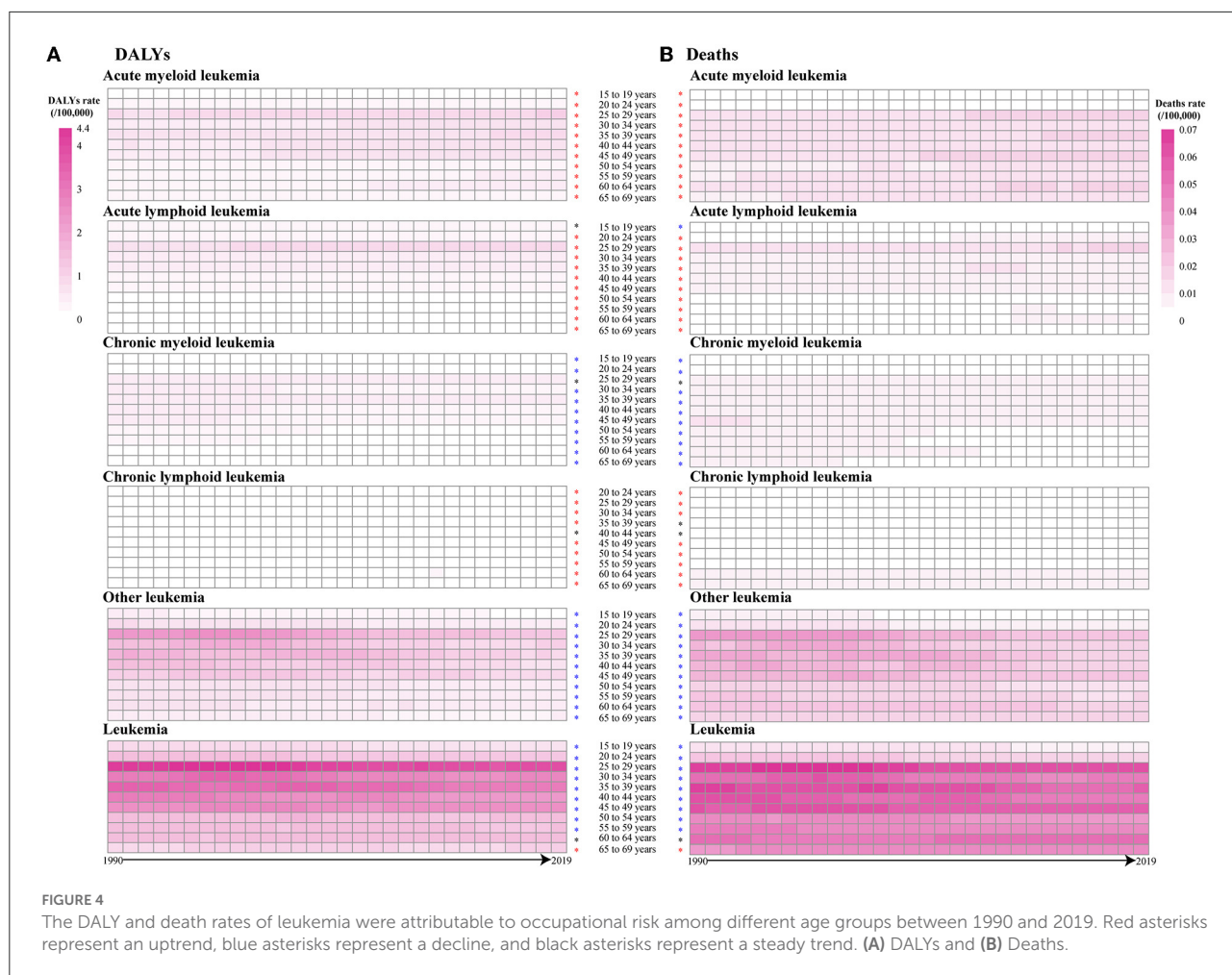
The global age-standardized DALYs and death rates of leukemia attributable to occupational risk were 1.5609, 95% UI: 0.7676–2.2942 for DALYs and 0.0326, 95% UI: 0.0161–0.0481 for deaths in 1990 and 1.3986, 95% UI: 0.669–2.0648 for DALYs and 0.0299, 95% UI: 0.0144–0.0445 for deaths in 2019. Male individuals had higher age-standardized rates than female individuals in leukemia attributable to occupational risk. Global age-standardized DALYs and death rates presented significantly decline trends with EAPCs [−0.38% (95% CI: −0.58 to −0.18%)

FIGURE 2
Differences in types of leukemia are attributable to occupational risk. **(A)** Acute lymphoid leukemia. **(B)** Acute myeloid leukemia. **(C)** Chronic lymphoid leukemia. **(D)** Chronic myeloid leukemia. **(E)** Other leukemia.

FIGURE 3
Age-standardized DALY and death rates of different types of leukemia attributable to occupational risk among SDI quintiles between 1990 and 2019. **(A)** Age-standardized DALY and death rates of leukemia are attributable to occupational risk globally. **(B)** High-SDI countries. **(C)** Higher-middle-SDI countries. **(D)** Middle-SDI countries. **(E)** Lower-middle-SDI countries. **(F)** Low-SDI countries. SDI, social development index. The red asterisk represents a significant rise trend, and the blue asterisk represents a significant decrease trend.

for DALYs and −0.30% (95% CI: −0.45 to −0.146%) for death] (Table 1). The highest age-standardized DALYs and death rates were observed in the regions of Andean Latin America, Central Latin America, and the Caribbean, whereas the lowest age-standardized incidence rates were seen in Southern sub-Saharan Africa (Figures 1A,B). The most pronounced increase in age-standardized DALYs and death rates was detected in the regions of Latin America and the Caribbean (Andean Latin America, Central Latin America, and the Caribbean), sub-Saharan Africa (Eastern sub-Saharan Africa and Western sub-Saharan Africa), and Southeast Asia and Oceania (Figures 1C,D, Table 1).

Impact of occupational risk on each leukemia

In 2019, ALL and AML were the leading causes of leukemia attributable to occupational risk-related DALYs and death rates. Both ALL and AML attributable to occupational risk were heavy in Central Latin America, Andean Latin America, and Southern Latin America (Figure 2, Supplementary Table 1). Globally, the age-standardized DALYs and death rates of ALL, AML, and CLL were presented a significantly increase trends with EAPCs [0.78% (95% CI: 0.65–0.91%), 0.87% (95% CI: 0.81–0.93%), and 0.66% (95% CI: 0.51–0.81%) for DALYs, respectively, and

FIGURE 4
The DALY and death rates of leukemia were attributable to occupational risk among different age groups between 1990 and 2019. Red asterisks represent an uptrend, blue asterisks represent a decline, and black asterisks represent a steady trend. **(A)** DALYs and **(B)** Deaths.

0.75% (95% CI: 0.68–0.82%), 0.96% (95% CI: 0.91–1.01%), and 0.55% (95% CI: 0.43–0.68%) for death, respectively], whereas the age-standardized DALYs and death rates of CML and other leukemia were significantly decreased. For SDI quintiles, except for the high SDI level region, the ALL, AML, and CLL were significantly increased in other SDI levels region (Figure 3, Supplementary Table 2).

Leukemia attributable to occupational risk age distribution structure

We analyzed the DALYs and death rates of leukemia attributable to occupational risk in three different age groups. The results indicated that most DALYs and deaths occurred in 25–29 years in the globe. Overall, the leukemia attributable to occupational risk was significantly increased in people aged 65–69 years [0.42% (95% CI: 0.30–0.55%) for DALYs and 0.38% (95% CI: 0.26–0.51%) for death]. The burdens of ALL, AML, and

CLL were increased in almost all age groups while decreased in CML and other leukemia (Figure 4).

Relationship between SDI and the burdens of leukemia attributable to occupational risk

In 2019, the highest age-standardized rates of leukemia attributable to occupational risk-related deaths and DALYs were observed in countries in the Middle-SDI [1.6778 (95% UI: 0.7894–2.4881) DALYs per 100,000 people and 0.0348 (95% UI: 0.0164–0.052) deaths per 100,000 people]. Figure 5 and Supplementary Figure 1 show the changes in age-standardized DALYs and death rates across the SDI by region from 1990 to 2019. Five regions with the highest SDI exhibited a decline in the age-standardized rate of leukemia attributable to occupational risk-related DALYs and deaths, whereas five regions with the lowest SDI experienced an increasing trend. The regions with
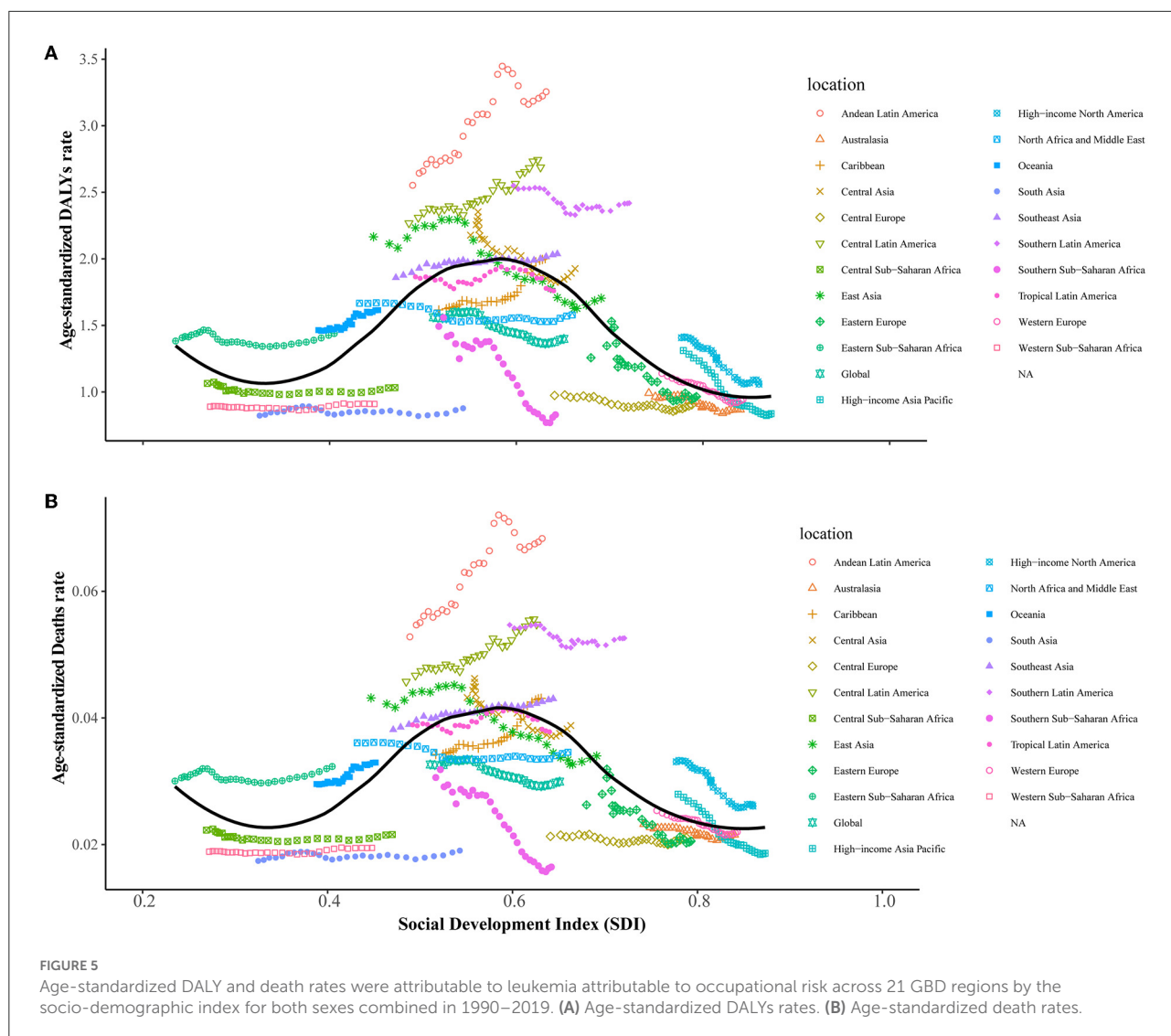
FIGURE 5
Age-standardized DALY and death rates were attributable to leukemia attributable to occupational risk across 21 GBD regions by the socio-demographic index for both sexes combined in 1990–2019. **(A)** Age-standardized DALYs rates. **(B)** Age-standardized death rates.

middle SDI show greatly varied. The associations between age-standardized DALYs and death rates and SDI across countries in 2019 are shown in Supplementary Figure 1.

Discussion

In this study, we reported the disease burden of leukemia attributable to occupational risk-related deaths and their trends from 1990 to 2019 at the global, regional, and country levels. Our findings showed several key points. Changes between different countries and regions in the burden and trends in total and particular leukemia attributable to occupational risk-related deaths across the globe were found in our research. In general, regions of Andean Latin America, Central Latin America, and the Caribbean were the so-called hotspot regions with the highest age-standardized rates of total leukemia attributable to

occupational risk-related deaths in 2019. Overall, most countries and regions showed a decrease in age-standardized DALYs and death rates. The DALYs and deaths of leukemia caused by occupational risk in elderly people is higher than that in other age groups, and the burdens are on the rise.

We analyzed the epidemiological trends of leukemia attributable to occupational risk by calculating the EAPC values from 1990 to 2019. As everyone knows, aging is an important factor contributing to leukemogenesis. Accompanied by aging gene mutations, changes in internal environmental homeostasis and mitochondrial dysfunction make the risk of leukemia higher in the elderly than in the young people (32–35). The marked increase in leukemia attributable to occupational risk in Latin America in terms of deaths and DALYs can be partially explained by the fact that humans in these countries and regions are mostly engaged in physical labor and have more opportunities to come into contact with toxic substances such as formaldehyde and

benzene. Besides, long-term poverty, poor access to healthcare, a lower awareness regarding occupational risk, inadequate prevention measures and screening, and a lower proportion of treatment together make low-income countries more susceptible to leukemia attributable to occupational risk than high-income countries (36–38). Therefore, in the subsequent campaign to eliminate leukemia attributable to occupational risk, more attention and health resources were warranted in developing countries and low-income regions.

Of note, our research found that, among all leukemia caused by occupational risk, the age-standardized DALYs and death rates were particularly observed in ALL and AML. The possible reasons can be listed as follows. First, the standard of leukemia classification has changed. For example, the World Health Organization (WHO) classification (2, 39), recognized as a standard for disease diagnosis and public health monitoring worldwide, has been revised from the primary to the 5th edition during the past 60 years (2). French-American-British (FAB) classification (40) and MICM classification (Morphology, Immunology, Cytogenetics, and Molecular) classification (41). Meanwhile, the diagnostic criteria for leukemia have also changed (42, 43). In terms of the countries and regions' distribution of these two kinds of leukemia, in Mexico and Latin America, the age-standardized DALYs and death rates were the highest, possibly because of the most common of these two types of leukemia in young adults and regional economic development. Thus, accurate surveillance data were important for developing a prevention-and-control program and providing valuable countermeasures to estimate the impact of those programs (44, 45). Elderly people were found to have disproportionately high DALYs and death rates in total leukemia attributable to occupational risk-related deaths, which might be due to age factors. For one thing, the DALYs and death rates of leukemia will increase with age, so the DALYs and death rates of the elderly will be higher than that of young adults. For another, if the elderly were exposed to toxic and harmful substances such as formaldehyde and benzene during adolescence, these substances will not immediately cause reactions after exposure but will slowly accumulate in the body, and symptoms will slowly emerge with age (46, 47). Our findings call for an urgent need to accelerate efforts to reduce leukemia attributable to the occupational risk burden in elderly people. Male individuals generally had higher age-standardized DALYs and death rates than female individuals for leukemia attributable to occupational risk-related deaths, possibly because men were the main part of social labor and were more engaged in heavy physical labor, thus, they had more chances to contact toxic and harmful substances. In addition, the burden of leukemia itself is higher in men than in women (48, 49).

Most countries had a decrease in age-standardized rates of DALYs and death rates for leukemia attributable to occupational risk-related deaths, whereas the absolute DALYs and death cases increased from 1990 to 2019. Leukemia attributable to occupational risk-related deaths still represents a global public health challenge, especially in Latin America and other developing countries, where more attention and health prevention services are warranted. Our study also suggested an upward trend of leukemia attributable to occupation risk among elderly people. ALL, AML, and CLL showed an upward trend in almost all age groups. Thus, there remains an urgent need to accelerate efforts to reduce leukemia attributable to occupational risk-related death burden in this population and specific causes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

WX designed the study. DX, CC, HS, YY, and YX accessed and verified the data. XY, HT, AL, and JJ analyzed the data and interpreted the results. YS, YH, XT, and DC wrote the manuscript. All authors revised the manuscript from the preliminary draft to submission.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1015861/full#supplementary-material

SUPPLEMENTARY FIGURE 1

Age-standardized DALY and death rates were attributable to leukemia attributable to occupational risk across countries and territories by the

socio-demographic index for both sexes combined in 2019. **(A)** Age-standardized DALYs rates. **(B)** Age-standardized death rates.

SUPPLEMENTARY TABLE 1

Differences in types of leukemia attributable to occupational risk in 21 GBD regions.

SUPPLEMENTARY TABLE 2

The trends of different types of leukemia attributable to occupational risk among SDI quintiles between 1990 and 2019.

References

1. Li J, Su H, Chen H, Futscher BW. Optimal search-based gene subset selection for gene array cancer classification. *IEEE Trans Inf Technol Biomed.* (2007) 11:398–405. doi: 10.1109/TITB.2007.892693

2. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the world health organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia.* (2022) 36:1703–19. doi: 10.1038/s41375-022-01613-1

3. Pathinarupothi RK, Durga P, Rangan ES. Data to diagnosis in global health: a 3P approach. *BMC Med Inform Decis Mak.* (2018) 18:78. doi: 10.1186/s12911-018-0658-y

4. Schwalbe EC, Lindsey JC, Nakjang S, Crosier S, Smith AJ, Hicks D, et al. Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: a cohort study. *Lancet Oncol.* (2017) 18:958–71. doi: 10.1016/S1470-2045(17)30243-7

5. Duncavage EJ, Schroeder MC, O'Laughlin M, Wilson R, MacMillan S, Bohannon A, et al. Genome sequencing as an alternative to cytogenetic analysis in myeloid cancers. *N Engl J Med.* (2021) 384:924–35. doi: 10.1056/NEJMoa2024534

6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* (2019) 69:7–34. doi: 10.3322/caac.21551

7. Song X, Peng Y, Wang X, Chen Y, Jin L, Yang T, et al. Incidence, survival, and risk factors for adults with acute myeloid leukemia not otherwise specified and acute myeloid leukemia with recurrent genetic abnormalities: analysis of the surveillance, epidemiology, and end results (SEER) database, 2001-2013. *Acta Haematol.* (2018) 139:115–27. doi: 10.1159/000486228

8. Qiu KY, Liao XY, Liu Y, Huang K, Li Y, Fang JP, et al. Poor outcome of pediatric patients with acute myeloid leukemia harboring high FLT3/ITD allelic ratios. *Nat Commun.* (2022) 13:3679. doi: 10.1038/s41467-022-31489-9

9. Sliwa-Tytko P, Kaczmarska A, Lejman M, Zawitkowska J. Neurotoxicity associated with treatment of acute lymphoblastic leukemia chemotherapy and immunotherapy. *Int J Mol Sci.* (2022) 23:5515. doi: 10.3390/ijms23105515

10. Prabhakar SK, Ryu S, Jeong IC, Won DO. A dual level analysis with evolutionary computing and swarm models for classification of leukemia. *Biomed Res Int.* (2022) 2022:2052061. doi: 10.1155/2022/2052061

11. Varghese JV, Sebastian EM, Iqbal T, Tom AA. Pesticide applicators and cancer: a systematic review. *Rev Environ Health.* (2021) 36:467–76. doi: 10.1515/reveh-2020-0121

12. Proceedings of the IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Epstein-Barr virus and kaposi's sarcoma herpesvirus/human herpesvirus 8. Lyon, France, 17-24 June 1997. *IARC Monogr Eval Carcinog Risks Hum.* (1997) 70:1–492.

13. Zheng Y, Yu Q, Lin Y, Zhou Y, Lan L, Yang S, et al. Global burden and trends of sexually transmitted infections from 1990 to 2019: an observational trend study. *Lancet Infect Dis.* (2022) 22:541–51. doi: 10.1016/S1473-3099(21)00448-5

14. Driscoll TR, Carey RN, Peters S, Glass DC, Benke G, Reid A, et al. The Australian work exposures study: prevalence of occupational exposure to formaldehyde. *Ann Occup Hyg.* (2016) 60:132–8. doi: 10.1093/annhyg/mev058

15. Vecchio D, Sasco AJ, Cann CI. Occupational risk in health care and research. *Am J Ind Med.* (2003) 43:369–97. doi: 10.1002/ajim.10191

16. Checkoway H, Boffetta P, Mundt DJ, Mundt KA. Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies. *Cancer Causes Control.* (2012) 23:1747–66. doi: 10.1007/s10552-012-0055-2

17. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Chemical agents and related occupations. *IARC Monogr Eval Carcinog Risks Hum.* (2012) 100:9–562.

18. Baan R, Grosse Y, Straif K, Secretan B, El Ghissassi F, Bouvard V, et al. A review of human carcinogens—part F: chemical agents and related occupations. *Lancet Oncol.* (2009) 10:1143–4. doi: 10.1016/S1470-2045(09)70358-4

19. Collins JJ, Lineker GA. A review and meta-analysis of formaldehyde exposure and leukemia. *Regul Toxicol Pharmacol.* (2004) 40:81–91. doi: 10.1016/j.yrtph.2004.04.006

20. Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. *Mutat Res.* (2009) 681:150–68. doi: 10.1016/j.mrrev.2008.07.002

21. Blue I, Harpham T. The world bank world development report 1993: investing in health. Reveals the burden of common mental disorders, but ignores its implications. *Br J Psychiatry.* (1994) 165:9–12. doi: 10.1192/bjp.165.1.9

22. GBD Tuberculosis Collaborators. Global regional, and national burden of tuberculosis, 1990-2016: results from the global burden of diseases, injuries, and risk factors 2016 study. *Lancet Infect Dis.* (2018) 18:1329–49. doi: 10.1016/S1473-3099(18)30625-X

23. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet.* (2020) 396:1204–22. doi: 10.1016/S0140-6736(20)30925-9

24. Wang H, Zhao S, Wang S, Zheng Y, Wang S, Chen H, et al. Global magnitude of encephalitis burden and its evolving pattern over the past 30 years. *J Infect.* (2022) 84:777–87. doi: 10.1016/j.jinf.2022.04.026

25. Zhao S, Wang H, Chen H, Wang S, Ma J, Zhang D, et al. Global magnitude and long-term trend of ischemic heart disease burden attributed to household air pollution from solid fuels in 204 countries and territories, 1990-2019. *Indoor Air.* (2022) 32:e12981. doi: 10.1111/ina.12981

26. Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, et al. The lancet commission on pollution and health. *Lancet.* (2018) 391:462–512. doi: 10.1016/S0140-6736(17)32345-0

27. Vanka KS, Shukla S, Gomez HM, James C, Palanisami T, Williams K, et al. Understanding the pathogenesis of occupational coal and silica dust-associated lung disease. *Eur Respir Rev.* (2022) 31:210250. doi: 10.1183/16000617.0250-2021

28. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet.* (2018) 392:1923–94. doi: 10.1016/S0140-6736(18)32225-6

29. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* (2018) 392:1736–88. doi: 10.1016/S0140-6736(18)32203-7

30. Xie L, Shang ZJ. Oral cancer incidence, mortality, and mortality-to-incidence ratio are associated with human development index in China, 1990-2019. *Biomed Res Int.* (2022) 2022:6457840. doi: 10.1155/2022/6457840

31. Cao G, Liu J, Liu M. Global, regional, and national incidence and mortality of neonatal preterm birth, 1990-2019. *JAMA Pediatr.* (2022) 176:787–96. doi: 10.1001/jamapediatrics.2022.1622

32. Zjablovskaja P, Florian MC. Acute myeloid leukemia: aging and epigenetics. *Cancers.* (2019) 12:103. doi: 10.3390/cancers12010103

33. Kerk S, Lin L, Myers AL, Sutton DJ, Andren A, Sajjakulnukit P, et al. Metabolic requirement for GOT2 in pancreatic cancer depends on environmental context. *Elife.* (2022) 11:e73245. doi: 10.7554/eLife.73245

34. Wong CC, Wu JL, Ji F, Kang W, Bian X, Chen H, et al. The cholesterol uptake regulator PCSK9 promotes and is a therapeutic target in APC/KRAS-mutant colorectal cancer. *Nat Commun.* (2022) 13:3971. doi: 10.1038/s41467-022-31663-z

35. Gao M, Huang X, Wu Z, Wang L, Yuan S, Du Z, et al. Synthesis of a versatile mitochondria-targeting small molecule for cancer near-infrared fluorescent imaging and radio/photodynamic/photothermal synergistic therapies. *Mater Today Bio.* (2022) 15:100316. doi: 10.1016/j.mtbio.2022.100316

36. Aral SO, Fenton KA, Holmes KK. Sexually transmitted diseases in the USA: temporal trends. *Sex Transm Infect.* (2007) 83:257–66. doi: 10.1136/sti.2007.026245

37. Trani JF, Moodley J, Maw MTT, Babulal GM. Association of multidimensional poverty with dementia in adults aged 50 years or older in South Africa. *JAMA Netw Open.* (2022) 5:e224160. doi: 10.1001/jamanetworkopen.2022.4160

38. Rasella D, Alves FJO, Reboucas P, de Jesus GS, Barreto ML, Campello T, et al. Long-term impact of a conditional cash transfer programme on maternal mortality: a nationwide analysis of Brazilian longitudinal data. *BMC Med.* (2021) 19:127. doi: 10.1186/s12916-021-01994-7

39. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the world health organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia.* (2022) 36:1720–48. doi: 10.1038/s41375-022-01620-2

40. Paolillo R, Boulanger M, Gatel P, Gabellier L, De Toledo M, Tempe D, et al. The NADPH oxidase NOX2 is a marker of adverse prognosis involved in chemoresistance of acute myeloid leukemias. *Haematologica.* (2022) 107:2562–75. doi: 10.3324/haematol.2021.279889

41. Feng L, Li Y, Li Y, Jiang Y, Wang N, Yuan D, et al. Whole exome sequencing detects CHST3 mutation in patient with acute promyelocytic leukemia: a case report. *Medicine.* (2018) 97:e12214. doi: 10.1097/MD.0000000000012214

42. Mrozek, K. Molecular cytogenetics in acute myeloid leukemia in adult patients: practical implications. *Pol Arch Intern Med.* (2022) 132:16300. doi: 10.20452/pamw.16300

43. Kulp M, Siemund AL, Larghero P, Dietz A, Alten J, Cario G, et al. The immune checkpoint ICOSLG is a relapse-predicting biomarker and therapeutic target in infant t(4;11) acute lymphoblastic leukemia. *iScience.* (2022) 25:104613. doi: 10.1016/j.isci.2022.104613

44. Wang L, Wang Y, Jin S, Wu Z, Chin DP, Koplan JP, et al. Emergence and control of infectious diseases in China. *Lancet.* (2008) 372:1598–605. doi: 10.1016/S0140-6736(08)61365-3

45. Amato E, Riess M, Thomas-Lopez D, Linkevicius M, Pitkanen T, Wolkowicz T, et al. Epidemiological and microbiological investigation of a large increase in vibriosis, northern Europe, 2018. *Euro Surveill.* (2022) 27:2101088. doi: 10.2807/1560-7917.ES.2022.27.28.2101088

46. Protano C, Buomprisco G, Cammalleri V, Pocino RN, Marotta D, Simonazzi S, et al. The carcinogenic effects of formaldehyde occupational exposure: a systematic review. *Cancers.* (2021) 14:165. doi: 10.3390/cancers14010165

47. Mozzoni P, Pinelli S, Corradi M, Ranzieri S, Cavallo D, Poli D. Environmental/Occupational exposure to radon and non-pulmonary neoplasm risk: a review of epidemiologic evidence. *Int J Environ Res Public Health.* (2021) 18:10466. doi: 10.3390/ijerph181910466

48. Ren HM, Liao MQ, Tan SX, Cheng C, Zhu S, Zheng L, et al. Global, regional, and national burden of cancer in children younger than 5 years, 1990-2019: analysis of the global burden of disease study 2019. *Front Public Health.* (2022) 10:910641. doi: 10.3389/fpubh.2022.9 10641

49. Khorrami Z, Pourkhosravani M, Eslahi M, Rezapour M, Akbari ME, Amini H, et al. Multiple air pollutants exposure and leukaemia incidence in Tehran, Iran from 2010 to 2016: a retrospective cohort study. *BMJ Open.* (2022) 12:e060562. doi: 10.1136/bmjopen-2021-0 60562