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ORIGINAL PAPER

Acute lymphoblastic leukemia: an assessment of international incidence, survival, and disease burden

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Abstract
Purpose Acute lymphoblastic leukemia (ALL) is a rare hematological malignancy. With the recent introduction of a classification system for hematopoietic and lymphoid neoplasms, more comprehensive assessment of ALL epidemiology is now possible. In this study, we describe recent international incidence of ALL and project the annual number of diagnoses to 2025. We also estimate relative survival and average potential years of life lost (AYLL) to assess the societal burden of ALL.
Methods Age-specific incidence data for ALL from select cancer registries in different geographies were obtained from the International Agency for Research on Cancer's Cancer Incidence in Five Continents Database. Country-specific age-standardized rates were calculated to allow for direct comparisons between countries. ALL-specific mortality and relative survival data were only available from the United States (US) National Cancer Institute's Surveillance, Epidemiology, and End Results program; mortality rates were estimated for other countries.
Results The age-standardized incidence rate of ALL during 2003–2007 ranged from 1.08 to 2.12 per 100,000 person-years in selected countries. Incidence was generally higher in the Americas and Oceania and lower in Asia and Eastern Europe. In most countries, the incidence rate of ALL in children was approximately four times that in adults. Survival was particularly poor among adults. In selected countries, the estimated AYLL ranged from 30 to 48 years for all ages and from 23 to 39 years for adults.
Conclusions Although a rare disease, ALL presents a significant public health burden given poor survival outcomes among adults, AYLL, and its importance as the most common pediatric cancer.

Keywords Acute lymphoblastic leukemia · International · Incidence · Projections · Survival · Potential years of life lost

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Introduction

Acute lymphoblastic leukemia (ALL) is a rare hematological malignancy of the bone marrow in which precursor lymphoblasts, blocked at an early stage of differentiation, proliferate rapidly and supplant normal hematopoietic cells of the bone marrow. The incidence of ALL peaks sharply among children 1–4 years of age and gradually rises again among adults starting around age 50 [1]. ALL comprises <1 % of adult cancers, but represents the most common childhood malignancy, accounting for approximately 25 % of cancers and 80 % of all leukemias in children [1, 2]. The prognosis of ALL can be particularly poor, especially among adults. Although the cure rate in childhood ALL nears 90 % [3, 4], the same level of success has not been achieved in adult ALL. Despite complete remission rates exceeding 90 % with initial chemotherapy treatment [5, 6], the cure rate in adult ALL is only 20–40 % [5, 7, 8]; most adults with ALL eventually experience relapse, often within 1 year of their diagnosis, from which the median survival is only 4–8 months [9–11].

In 2001, the World Health Organization (WHO) produced a consensus-based classification system that defines

hematopoietic and lymphoid neoplasms based on distinct combinations of morphology, immunophenotype, genetic, molecular, and clinical features, thereby providing a framework for consistent identification of such malignancies internationally [12]. However, subtypes of leukemia, including ALL, are seldom distinguished in contemporary studies of global cancer incidence, mortality, and survival; instead, global epidemiologic measures of hematologic malignancies are often limited to broader categorizations of cancer, such as "leukemia" [13–15]. Furthermore, studies providing statistics on ALL are typically limited to children, do not differentiate between childhood and adult ALL, are based on older data, or are restricted to a single country or global region [2, 16–29].

The objectives of this study are to provide a comprehensive assessment of recent international incidence of childhood and adult ALL through 2007 and to estimate the number of future childhood and adult ALL diagnoses from 2015 to 2025. In addition, we approximate the incidence of major subtypes of adult ALL, describe current estimates of relative survival in childhood and adult ALL, and provide international estimates of average potential years of life lost (AYLL) due to ALL to assess the societal burden of this grievous illness.

Methods

Incidence data for ALL from select cancer registries in Asia, the Americas, Europe, and Oceania (Table 1) were obtained from three recent volumes of the International Agency for Research on Cancer's (IARC's) Cancer Incidence in Five Continents Volume X (CI5-X) database that covers the 5-year time period 2003–2007 [30]. For each registry, incident cases of ALL, categorized according to International Classification of Diseases, 10th Revision (ICD-10) code C91.0, and person-years were abstracted by age group (i.e., 5-year age groups 0–4, 5–9, and 10–14 years, and so on through 80–84 years, as well as a single group for persons 85 years and older). For countries without a national cancer registry, we aggregated data from regional registries to provide a proxy of national incidence. Crude age group-specific, childhood (0–19 years), adult (20–85+ years), and overall incidence rates were calculated for each registry and country. Data from CI5-X were used to provide estimates of global incidence rates of ALL in 21 selected countries across the four global regions. To enable making valid comparisons across countries with different age distributions, crude incidence rates were age-standardized to the World Health Organization's (WHO's) 2000–2025 world standard population [31].

In order to estimate the number of expected incident diagnoses of ALL in future years, we utilized country-specific population projections for 2015 through 2025, from The Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, *World Population Prospects: The 2012 Revision* [32]. Population figures were gathered by age group as described above. Since identification and reporting of ALL in cancer registries may have changed after the WHO developed its taxonomy of hematologic malignancies in 2001, measures of ALL incidence preceding the establishment of this classification system may not be comparable with measures that followed, and combining earlier (i.e., prior to 2001) with more recent data may misinform historical trends of ALL incidence. Therefore, in order to conservatively project annual ALL incidence in the coming years, we assumed that future age-specific incidence rates for each country would be the same as those reported in CI5-X. Thus, to project incident diagnoses of ALL for years 2015, 2020, and 2025, crude age group-specific incidence rates of ALL from CI5-X were multiplied by the population projections for each country; for countries without a national cancer registry, incidence rates from the aggregation of regional registry data were used. Within each calendar year, incidence estimates were summed across age groups to provide the number of projected diagnoses overall and separately for children and adults.

Incidence estimates of adult ALL for 2015 were further divided into major subtypes of ALL according to immunophenotype and Philadelphia chromosome status. Since information on immunophenotype and Philadelphia chromosome status is typically absent from cancer registry data, literature-based approximations of these disease characteristics were applied to our incidence estimates for 2015. Estimates were first divided according to immunophenotype, with approximately 80 % B-lineage and the remaining 20 % T-lineage [33–37]; B-lineage was further divided into Burkitt leukemia (5 % of adult ALL), which is treated differently from other forms of ALL, and precursor B cell ALL (75 % of adult ALL). Precursor B cell ALL estimates were then divided according to Philadelphia chromosome status, with approximately 23 % Philadelphia chromosome positive (Ph+) and the remaining 77 % Philadelphia chromosome negative (Ph−) [38]. To further describe the largest subgroup of adult ALL patients with a significant unmet medical need, we estimated the number of adults with incident Ph− precursor B cell ALL who will experience refractory or relapsed disease by applying proportions from published trial results to our incidence estimates [9, 39, 40].

Survival data from 18 cancer registries participating in the United States (US) National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program [41] were used to estimate 1- and 5-year relative survival. Survival data were limited to the US as the SEER

Table 1 Selected cancer registries from the cancer incidence in Five Continents, Volume X Database

Region	Country	Registries
Europe	Czech Republic	National
	Denmark	National
	France	Regional: Bas-Rhin, Calvados, Doubs, Haut-Rhin, Herault, Isere, Loire Atlantique, Manche, Somme, Tarn, and Vendee
	Germany	Regional: Hamburg, Munich, North Rhine, Bremen, Schleswig-Holstein, Brandenburg, Mecklenburg, Free State of Saxony, and Saarland
	Italy	Regional: Florence and Prato, Latina, Varese, Ferrara, Modena, Parma, Ragusa, Romagna, Torino, Veneto, Umbria, Sassari, Naples, Biella, Friuli-Venezia Giulia, Trento, Mantova, Genova, Reggio Emilia, Brescia, Milan, Salerno, Sondrio, Syracuse, Trapani, Nuoro, Catanzaro, Palerme, Alto Adige, Catania and Messina, Como, Lecco, and South Lombardy
	Poland	Regional: Cracow, Lower Silesia, Kielce, and Rzeszow
	Spain	Regional: Tarragona, Granada, Murcia, Navarra, Asturias, Basque Country, Mallorca, Albacete, Girona, Canary Islands, Cuenca, La Rioja, Ciudad Real
	Sweden	National
	UK	Regional: East Anglia/East of England, North Western, Oxford, South and Western, Thames, Trent, West Midlands, Northern and Yorkshire, Northern Ireland, Scotland, and Wales
Asia	China	Regional: Beijing, Qidong, Shanghai, Cixian, Jiashan, Wuhan, Zhongshan, Harbin City, Yanting, Haining, Jiaxing, Hong Kong, Yangcheng, and Macao
	Israel	National
	Japan	Regional: Hiroshima, Miyagi, Nagasaki, Osaka, Saga, Niigata, Fukui, and Aichi
	Republic of Korea	National
	Singapore	National
Oceania	Australia	Regional: Capital Territory, New South Wales, Northern Territory, Queensland, South, Tasmania, Victoria, and Western
	New Zealand	National
Americas	Argentina	Regional: Bahia Blanca, Cordoba, Mendoza, and Tierra del Fuego
	Brazil	Regional: Fortaleza, Goiania, Sao Paulo, Cuiaba, Aracaju, and Belo Horizonte
	Colombia	Regional: Cali, Bucaramanga, Manizales, and Pasto
	Costa Rica	National
	USA	SEER 18 (Alaska Native Tumor Registry, Atlanta, Connecticut, Detroit, Greater California, Greater Georgia, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Rural Georgia, San Francisco-Oakland, San Jose-Monterey, Seattle-Puget Sound, and Utah)

program database is currently the only population-based resource that provides survival data for ALL specific to 5-year age groups. To utilize the most recent information available in the SEER program, we obtained relative survival data for patients with a diagnosis of ALL in the SEER 18 database between 2003 and 2010 and followed through 2011. We excluded patients with ALL reported by death certificate or autopsy only and patients with unknown survival time. One- and 5-year relative survival estimates were provided for each age group, as well as for childhood, adult, and overall populations.

To estimate the projected AYLL from ALL in 2015, we obtained ALL-specific mortality rates for the 18 SEER cancer registries during the period 2003–2007 from the SEER mortality database [42]. ALL incidence rates were estimated from the SEER database for the corresponding 18 cancer registries and time period, and ratios of incidence to mortality rates for each 5-year age group were calculated. In order to approximate mortality rates for other countries, these ratios of incidence to mortality rates in the USA were assumed to be similar to those in other countries. Mortality rates were approximated by dividing age-specific incidence to mortality rate ratios by the corresponding age-specific incidence rates from CI5-X for the selected countries. These approximated country-specific mortality rates were multiplied by population projections to estimate the number of expected deaths from ALL in 2015. After extracting estimated life expectancies for each country from the Global Health Observatory data repository of the WHO [43], potential years of life lost (PYLL)

were calculated by multiplying the number of estimated ALL-specific deaths for a given 5-year age group by the remaining life expectancy for that group [44]. For each country, the total PYLL for children, adults, and the overall population were approximated by summing the PYLL across appropriate age groups. The AYLL from ALL for children, adults, and the overall population were then estimated as the total PYLL divided by the corresponding total number of estimated ALL deaths.

To evaluate whether our assumption of using US-based ratios of incidence to mortality rates provides fair approximations of mortality rates for other countries, particularly for the purpose of estimating the AYLL from ALL, we compared our estimated mortality rates with those for countries in which we were able to identify country-specific mortality data [45–49]. Specifically, we compared mortality rates for each 5-year age group, the distribution of mortality across age groups, and estimates of the AYLL from ALL.

Results

Age-specific incidence of ALL

Figure 1 shows incidence rates of ALL for 5-year age groups for a few countries (Australia, China, Costa Rica, Germany, Italy, Japan, and the USA) selected to represent the various geographic regions; age-specific incidence curves for the remaining countries included in this study followed the same pattern observed in the figure (results not shown). Incidence of ALL peaked in children aged 0–4 years and then decreased sharply among older children and adolescents before leveling off in young adults. Incidence was generally lowest between adult age groups 25–29 and 45–49 years, and increased gradually among older age groups starting among adults 50–54 years.

Overall incidence of ALL

In CI5-X, an approximately twofold difference in overall ALL age-standardized incidence was observed between Costa Rica (2.12 per 100,000 person-years) and the Czech Republic (1.08 per 100,000), the countries with the highest and lowest rates, respectively, among those we selected for our analyses (Fig. 2a). Generally, the age-standardized incidence of ALL was highest in the Americas and Oceania and lowest in Asia (except Singapore) and Eastern Europe (i.e., Czech Republic and Poland).

Incidence of ALL in children (0–19 years)

Among selected countries, Singapore reported the highest age-standardized incidence rate of childhood ALL (3.78 per 100,000 person-years) (Fig. 2b). Age-standardized incidence rates of >3.5 per 100,000 were also reported in Australia, Costa Rica, and Italy. Conversely, China

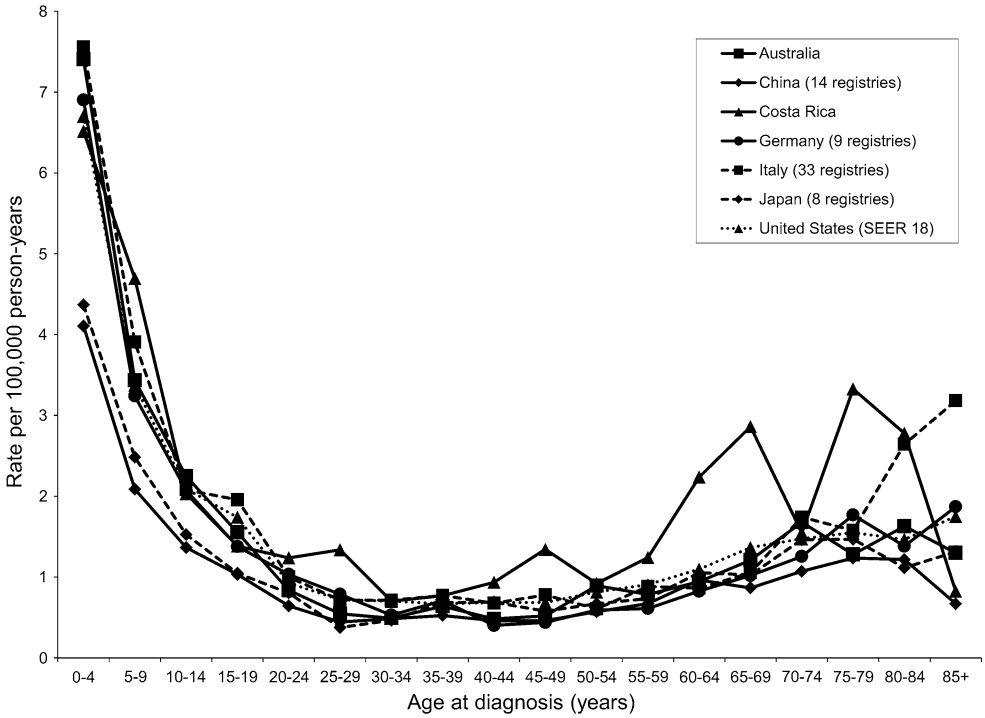

Fig. 1 Age-specific incidence rates (per 100,000 person-years) of acute lymphoblastic leukemia from 2003 to 2007 in selected countries

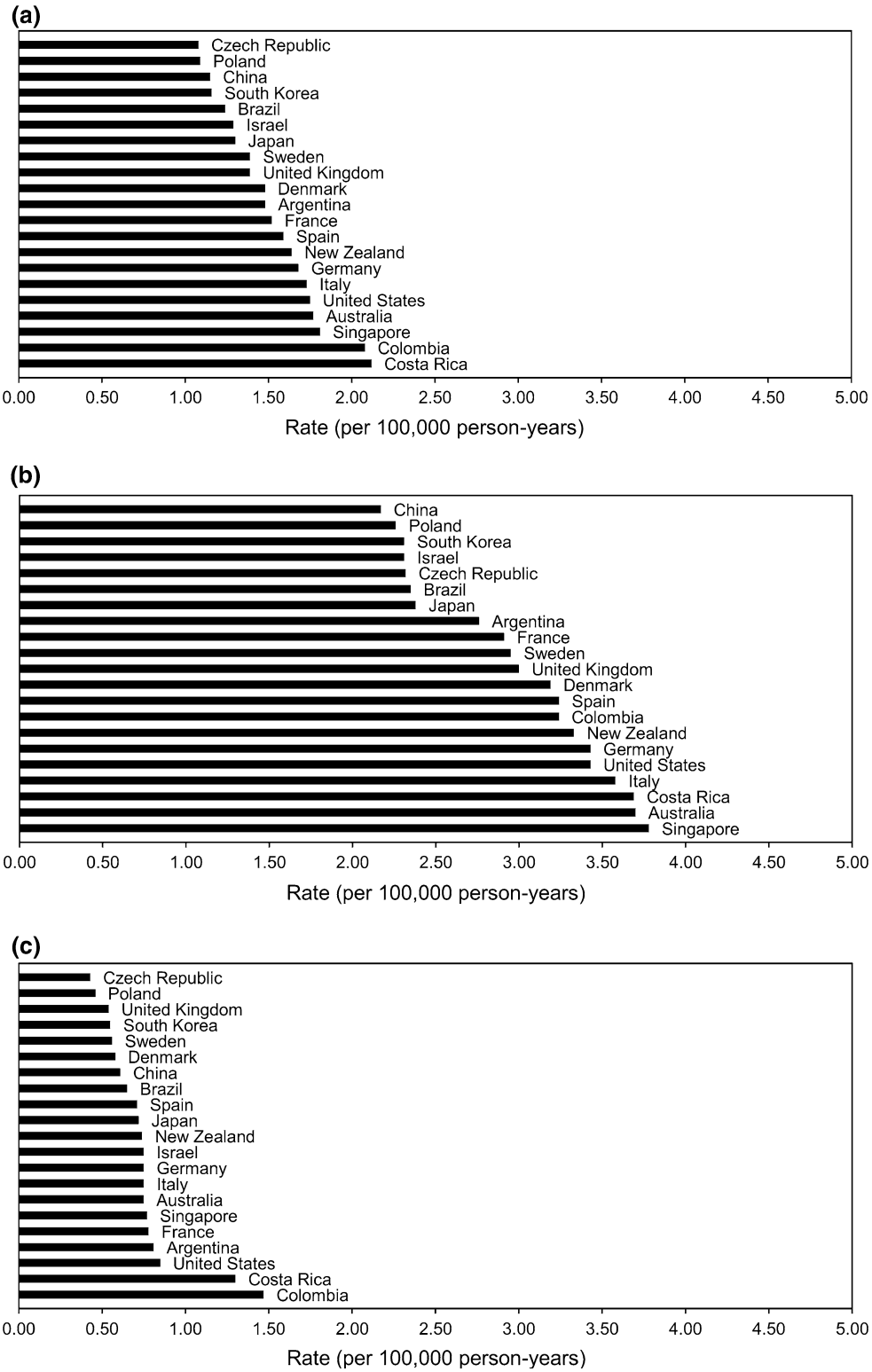

Fig. 2 Incidence rates of acute lymphoblastic leukemia (per 100,000 person-years) age-standardized to the WHO 2000–2025 world standard population (2003–2007). **a** Overall, **b** children (0–19 years), and **c** adults (20+ years)

reported the lowest age-standardized incidence rate of childhood ALL (2.17 per 100,000), while other Asian countries, the Czech Republic, and Poland also reported age-standardized rates of <2.4 per 100,000.

Incidence of ALL in adults (20+ years)

On average, the incidence rate of adult ALL among selected countries was roughly four times lower than the

corresponding incidence rate of childhood ALL (Fig. 2c). The age-standardized incidence of adult ALL was remarkably higher in Colombia and Costa Rica than in all other selected countries. There was greater than a threefold difference in the age-standardized incidence of adult ALL between Colombia (1.47 per 100,000) and the Czech Republic (0.43 per 100,000), the countries with the highest and lowest reported rates, respectively.

Projected incident diagnoses of ALL

Under the assumption that future age-specific incidence rates of ALL will be similar to those estimated in CI5-X for the 2003–2007 period, the projected annual number of incident diagnoses of ALL will generally increase between 2015 and 2025 in tandem with anticipated population increases over this time period (Table 2). Overall, proportional growth in the estimated number of incident diagnoses of ALL is highest for Australia, Colombia, and Singapore and lowest for Japan, where the total number of ALL diagnoses is projected to decrease over time. The number of incident diagnoses of childhood ALL is only expected to increase in a few countries (i.e., France, Sweden, the UK, Singapore, Australia, and the USA), whereas the number of incident diagnoses of adult ALL is projected to grow in each of the selected countries other than the Czech Republic, Denmark, Poland, and New Zealand.

Projected incidence of selected adult ALL subtypes

The projected incidence of adult ALL in 2015 for the USA and European Union Five (EU5), overall and by selected subtypes, is shown in Fig. 3. Between 2150 and 2370 and 1920–2120 incident diagnoses of adult ALL were projected for the USA and EU5, respectively. Of these, approximately 1720–1900 in the USA and 1540–1700 in the EU5 were estimated as B-lineage, the primary immunophenotype,

Table 2 Projected range of diagnoses of childhood and adult acute lymphoblastic leukemia from 2015 to 2025 by country

Population	2015		2020		2025	
	Children (0–19)	Adults (20+)	Children (0–19)	Adults (20+)	Children (0–19)	Adults (20+)
Europe						
Czech Republic	50–55	40–45	50–55	40–45	50–55	40–45
Denmark	40–45	25–30	40–45	25–30	40–45	25–30
France	430–480	410–450	440–480	430–470	440–490	440–490
Germany	460–510	550–600	460–510	550–610	450–510	560–620
Italy	390–430	410–460	380–420	420–470	370–410	430–480
Poland	170–190	140–160	170–190	140–150	170–190	140–160
Spain	300–330	270–300	290–320	280–310	280–300	290–320
Sweden	65–70	45–50	65–75	45–50	70–75	50–55
UK	430–470	280–310	440–480	290–320	440–490	300–330
Asia						
China	7070–7820	6230–6880	6990–7730	6540–7230	6640–7340	6930–7660
Israel	65–70	35–40	65–75	40–45	65–75	40–45
Japan	490–540	860–950	470–520	870–970	450–500	870–970
Singapore	40–45	30–35	45–50	35–40	45–50	40–45
South Korea	210–240	210–230	210–230	220–250	210–230	230–260
Oceania						
Australia	220–240	140–150	230–250	150–170	240–260	160–180
New Zealand	40–45	25–30	40–45	25–30	40–45	25–30
Americas						
Argentina	350–390	260–280	350–390	280–300	350–390	290–320
Brazil	1390–1530	850–940	1320–1460	950–1050	1270–1400	1040–1150
Colombia	540–600	420–470	540–600	480–530	530–590	540–590
Costa Rica	50–60	45–50	50–55	45–50	50–55	50–55
USA	2790–3080	2150–2370	2860–3160	2290–2530	2940–3250	2430–2680

Projected range encompasses ±5 % of the estimated number of incident diagnoses. Projections are rounded to the nearest 10 except projections <100 which are rounded to the nearest 5

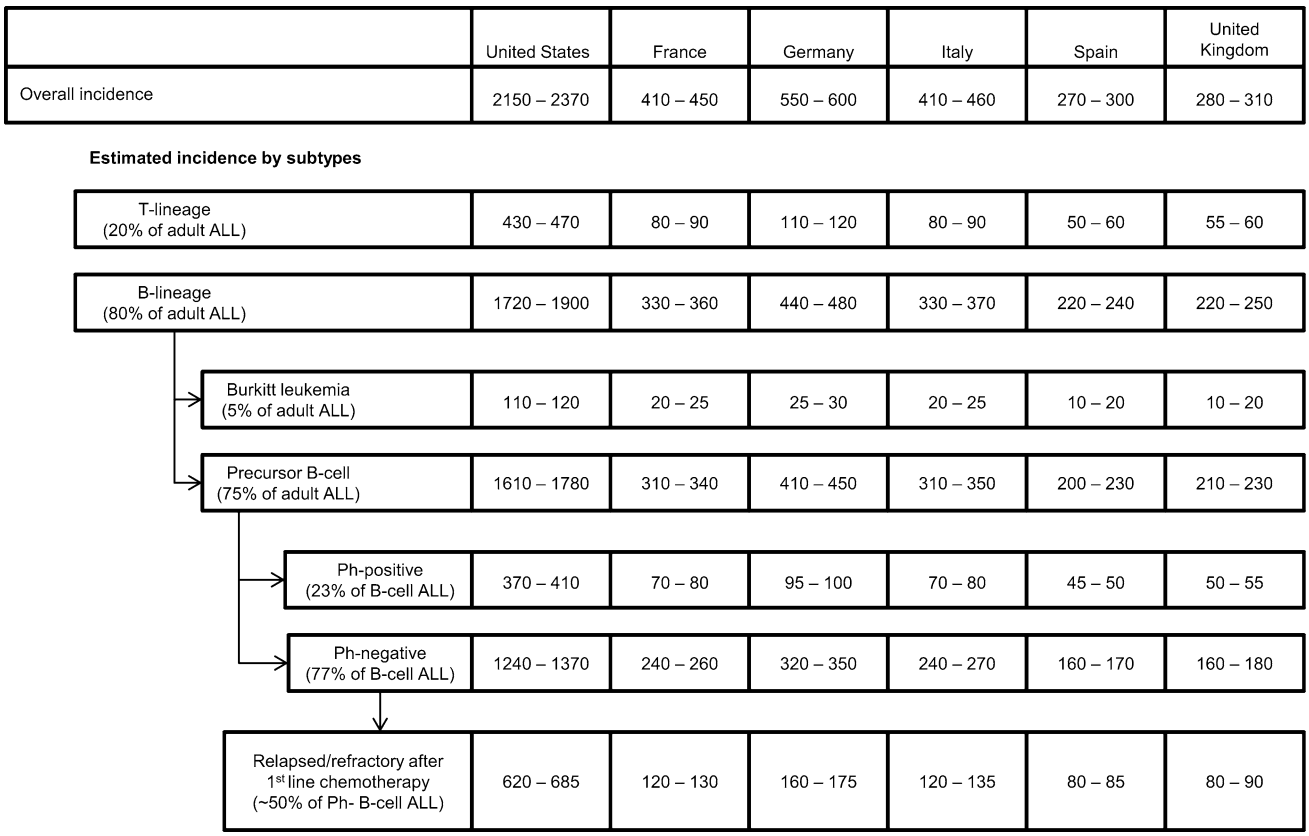

Fig. 3 Projected ranges of incidence overall and for selected subtypes of adult acute lymphoblastic leukemia (ALL) in the USA and European Union Five (EU5), 2015

including 1610–1780 in the USA and 1440–1600 in the EU5 as precursor B cell ALL specifically. Among the projections for precursor B cell ALL, the majority were estimated as Ph− (1240–1370 in the USA and 1120–1230 in the EU5), and of those, an estimated 50 % (620–685 in the USA and 560–615 in the EU5) will be refractory to initial chemotherapy or eventually experience relapse.

Relative survival

Among patients diagnosed with ALL in one of the 18 SEER regions of the USA between 2003 and 2010 and followed through 2011, the overall 1- and 5-year relative survival rates were 82.7 and 66.3 %, respectively (Fig. 4). Infants (<1 year) had less favorable survival than older children (1–4, 5–9, and 10–14 years) and adolescents (15–19 years). This aside, relative survival was higher among children (0–19 years) than in adults (20+ years). Beginning at ages 1–4 years, relative survival decreased progressively with increasing age at ALL diagnosis, with a particularly notable decline in 5-year survival beginning at ages 20–24 years. Five-year relative survival was <50 % in adults 20–24 years at diagnosis and declined to <30 % among adults 50–54 years and older. Survival in adults 65 years and older was the poorest with 1- and 5-year relative survival rates of 35 and 12 %, respectively. Relative survival estimates are also provided in Table 3.

Average potential years of life lost

Estimated AYLL due to ALL in 2015 based on approximated mortality rates are displayed in Table 4 for each population (i.e., overall, children, and adults) with countries ordered according to life expectancy from birth. Overall, the estimated AYLL range from a low of 29.8 years in Poland to a high of 48.2 years in Israel with approximately half of the selected countries having estimated AYLL of 35–40 years. Among children, the estimated AYLL vary from 66.5 years in Brazil to 75.8 years in Japan. For most countries, the AYLL in children were estimated to be between 70 and 75 years. Among adults, AYLL range from 22.5 years in Poland to 38.9 years in

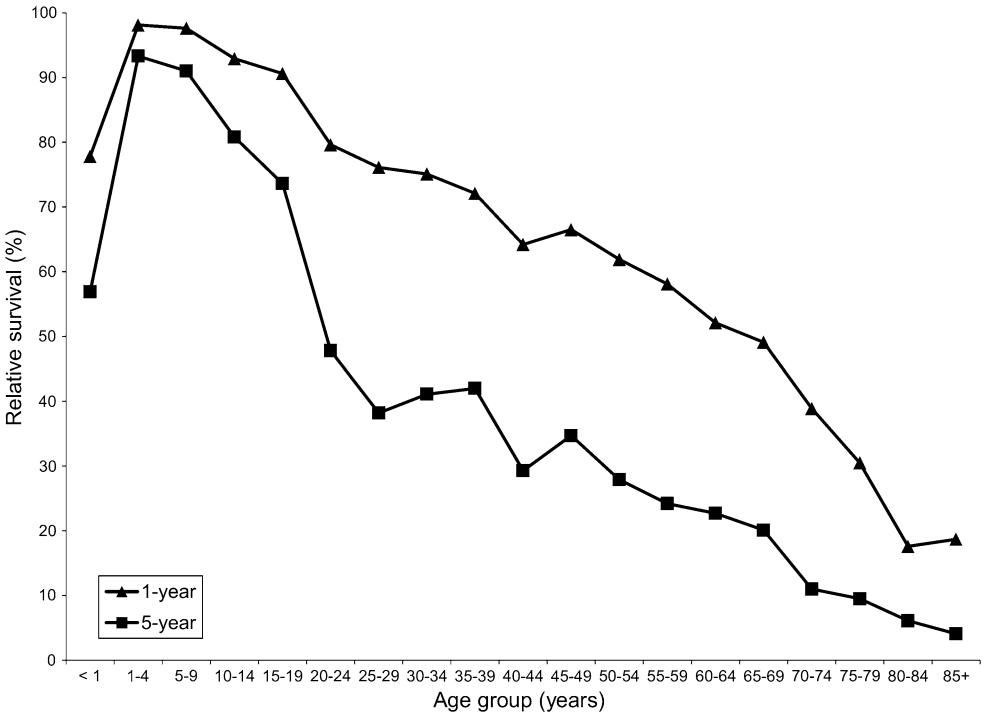

Fig. 4 Relative survival rates by age at diagnosis among patients diagnosed with acute lymphoblastic leukemia between 2003 and 2010 and followed through 2011 in the US Surveillance, Epidemiology, and End Results (SEER) program

Table 3 Relative survival rates for patients diagnosed with acute lymphoblastic leukemia between 2003 and 2010 and followed through 2011 in the US SEER program, by age at diagnosis

Age group	*n*	1-Year relative survival		5-Year relative survival	
		Rate (%)	95 % CI	Rate (%)	95 % CI
Birth–<1 years	211	77.8	71.1, 83.1	56.9	49.0, 64.1
1–4	3329	98.1	97.5, 98.5	93.3	92.1, 94.3
5–9	1791	97.6	96.7, 98.2	91.0	89.2, 92.5
10–14	1152	92.9	91.3, 94.3	80.8	77.9, 83.3
15–19	949	90.6	88.5, 92.4	73.6	70.1, 76.7
20–24	509	79.6	75.6, 83.0	47.8	42.5, 53.0
25–29	366	76.1	71.1, 80.3	38.2	32.1, 44.3
30–34	338	75.1	70.0, 79.5	41.1	34.8, 47.3
35–39	341	72.1	66.8, 76.8	42.0	35.8, 48.1
40–44	353	64.2	58.6, 69.2	29.3	23.7, 35.2
45–49	374	66.5	61.2, 71.2	34.7	29.0, 40.4
50–54	385	61.9	56.6, 66.7	27.9	22.7, 33.3
55–59	355	58.1	52.5, 63.2	24.2	18.7, 30.0
60–64	321	52.1	46.2, 57.6	22.7	17.2, 28.8
65–69	295	49.1	42.8, 55.0	20.1	14.6, 26.3
70–74	213	38.9	32.0, 45.8	11.0	6.0, 17.7
75–79	170	30.5	23.5, 37.9	9.5	4.8, 16.1
80–84	143	17.6	11.5, 24.8	6.1	1.9, 13.9
85+	129	18.7	12.0, 26.5	4.1	0.8, 12.0
Birth–19 years	7342	95.6	95.1, 96.1	87.1	86.2, 88.0
20+ years	4292	60.6	59.1, 62.1	30.1	28.4, 31.7
20–64 years	3342	67.9	66.2, 69.6	34.9	33.0, 36.9
65+ years	950	34.5	31.3, 37.8	12.4	9.7, 15.4
Total	11,634	82.7	82.0, 83.4	66.3	65.3, 67.3

Table 4 Estimated average years of life lost to acute lymphoblastic leukemia in 2015, by age group

Population	Life expectancy at birth[a]	Average years of life lost from ALL		
		Children (1–19 years)	Adults (20+ years)	Overall
Japan	84	75.8	27.0	31.2
Australia	83	75.3	30.8	39.9
Italy	83	75.3	26.6	32.9
Singapore	83	74.3	35.7	43.4
France	82	73.8	28.6	35.6
Israel	82	73.5	38.9	48.2
New Zealand	82	74.0	33.5	42.4
Spain	82	74.8	30.1	37.3
Sweden	82	75.2	28.5	37.0
Germany	81	73.0	25.9	31.7
South Korea	81	73.1	34.0	40.5
UK	81	73.3	28.2	37.2
Denmark	80	72.2	28.8	37.6
Costa Rica	79	72.3	34.7	41.8
Colombia	79	72.1	33.4	41.0
USA	79	70.8	29.2	36.9
Czech Republic	78	70.7	24.5	31.8
Poland	77	68.8	22.5	29.8
Argentina	76	71.6	25.7	35.4
China	75	68.6	29.8	36.3
Brazil	74	66.5	28.5	37.8

[a] Estimates of life expectancy at birth in 2012 from the WHO Global Health Observatory [43]

Israel with approximately half of selected countries having estimated AYLL of 25–30 years.

For countries with available data, mortality rates from country-specific sources and those approximated using SEER-based incidence to mortality rate ratios and incidence rates from CI5-X are provided in Table 5 in "Appendix." Compared to estimates from country-specific sources for Australia, Denmark, Spain, and the UK, approximated mortality rates were generally higher for most age groups, resulting in more estimated deaths and PYLL. The distribution of the number of deaths across age groups was similar between estimates from country-specific sources and those that we approximated. Among adults, approximated mortality rates estimate 18–23, 33–40, and 40–49 % of ALL deaths occur among those aged 20–39, 40–64, and 65+ years, respectively; in comparison, country-specific sources estimate 16–24, 30–34, and 46–53 % of adult ALL deaths occur among these age groups, respectively. Estimates of the AYLL from ALL were also quite similar between those we approximated and those from country-specific sources. Absolute differences in estimates ranged from 0.1 to 0.8 years for childhood ALL, 0.3–1.8 years for adult ALL, and 1.2–2.4 years for ALL overall.

Discussion

In this study, we provide a comprehensive assessment of the international incidence of childhood and adult ALL using data more recent than previously available and that followed the introduction of the 2001 WHO classification system for hematologic malignancies. In addition, we estimate the number of future childhood and adult ALL diagnoses, including approximations for selected subtypes of adult ALL, describe current estimates of relative survival in childhood and adult ALL, and provide international estimates of the AYLL from ALL to illustrate the public health burden of this grievous illness.

In agreement with previous studies [2, 50], the incidence of ALL varied considerably by age with some variations across geographic regions. In the majority of selected countries, the age-standardized incidence rate of ALL among children was three to four times the incidence rate among adults. However, the variation in international incidence was minimal, considering that the majority of selected countries reported an age-standardized incidence rate between 1.1 and 1.8 per 100,000 person-years; only

Colombia and Costa Rica reported an age-standardized incidence rate of >1.8 per 100,000. The elevated overall incidence rates in Colombia and Costa Rica largely reflect the markedly higher frequency of adult ALL in these two countries and are consistent with past reports of elevated incidence among countries in Latin America and Hispanic populations in the USA [2, 20, 28, 51]. Likewise, the lower rates of ALL observed in the Czech Republic and Poland are also in line with findings from earlier studies in which both the overall incidence of ALL [23] and the incidence of childhood ALL [27] were less frequent in Eastern Europe relative to other European regions. Of note, however, a recent study in Croatia [52] reported an age-standardized incidence rate of ALL >1.6 per 100,000 person-years, which was higher than the rate reported for Poland and the Czech Republic in this study.

Quantification of the projected number of annual ALL diagnoses is central to understanding the societal burden of this disease. In particular, estimates of the number of annual diagnoses for subgroups of patients with a significant unmet medical need can inform research, health policy, and healthcare resource allocation priorities. Here, we provided projections of the incidence of overall, childhood, and adult ALL, including estimates for select subtypes of adult ALL. Based on expected population changes, we projected that the number of diagnoses of ALL in the majority of selected countries will remain fairly stable or increase slightly between 2015 and 2025. However, with the aging of populations across the globe, we estimated that the number of diagnoses of childhood ALL will decrease over this time period, particularly in Brazil, China, and Japan where the populations of children are expected to decline. Conversely, with an increase in the number of adults, especially older adults, projected for most countries, we estimated that the number of diagnoses of adult ALL will increase between 2015 and 2025; this projection indicated an increase in adult ALL diagnoses of at least 20 % in Brazil, Colombia, and Singapore in particular, but estimated an increase of <15 % for all other selected countries. Given that recent studies [21, 52, 53] reported trends of stable incidence for ALL in several countries, we believe that our use of incidence rates from CIV to X to project the number of diagnoses of ALL from 2015 to 2025 provides conservative estimates of the incidence of ALL in selected countries. In addition, by using incidence rates specific to 5-year age groups, we allowed the incidence rate of ALL overall and for the broader age groupings (i.e., childhood and adults) to still vary over time based on the projected changes in the age distribution of the populations.

We showed that survival rates in ALL differ markedly by age. In particular, infants and older adults have less favorable survival than other children, adolescents, and younger adults. Differences in survival may be partly explained by variation in other prognostic factors and the treatments utilized across age groups [54]. For example, pediatric patients are typically treated more aggressively than adults, and Philadelphia chromosome-positive ALL, which is more common among adults [55], has traditionally been associated with a particularly poor prognosis. Furthermore, the low survival observed among adults 65 and older may reflect greater comorbidity and frailty in older patients. In turn, greater comorbidity and frailty may decrease the tolerability of treatment-associated toxicities and prohibit the use of standard treatment regimens in older patients. Nevertheless, poor survival among adults with ALL, including both younger and older adults (5-year relative survival was <50 % even among adults 20–24 years of age) further illustrates the burden of this disease and highlights the unmet medical need to develop better treatments for this patient population.

Although ALL is a rare form of cancer, the peak in incidence among children and poor long-term survival among adults contributes to a comparatively high AYLL that exceeds those of other more common malignancies. In the UK, for example, we estimated that adults who die with ALL lose 28 years of life on average, higher than the AYLL reported for other malignancies, including non-Hodgkin lymphoma (13 years) and prostate (6 years), lung (12 years), and breast (14 years) cancers [44]. Similarly, in selected countries, the AYLL estimated for adults with ALL are greater than the AYLL reported for adults with myeloma (17 years) in North America, Japan, and Europe [56]. The higher AYLL in ALL relative to other cancers among adults illustrate that adult ALL is largely a disease of younger, working age adults; in the SEER mortality database [42] from 2003 to 2007, more than 40 % of adult ALL deaths occurred among adults <50 years of age and approximately 60 % of adult ALL deaths occurred in adults under age 65 (results not shown). Thus, although the annual incidence rate, number of deaths, and the total PYLL for ALL are small relative to other cancer types, the burden of ALL is remarkably high in comparison when we consider the poor survival outcomes in adults, the relatively young age at diagnosis, and the AYLL among patients who die of this grievous disease.

It should be noted that our estimates of AYLL from ALL varied across countries, particularly among adults. However, the variation in AYLL across countries is likely due in large part to differences in life expectancy and the age distribution of the population, rather than differences in age-specific mortality due to ALL. For example, the difference in life expectancy at birth between Japan and

Brazil (10 years) is similar to the difference in AYLL among children who die from ALL in these countries (~9 years); in general, as life expectancy at birth decreases, so does the estimated AYLL among children. Similarly, estimates of AYLL from ALL among adults are generally higher in countries where adults 65 and older make up smaller proportions of the adult population. For example, adults 65 and older make up <20 % of the adult population and 20 % or less of the incidence of adult ALL in Israel, Singapore, and Costa Rica, the countries with the three highest estimates for AYLL among adults; conversely, adults 65 and older make up over 25 % of the adult population and approximately 45 % or more of the incidence of adult ALL in Germany, Italy, and Japan, countries with three of the lowest estimates for AYLL. Thus, despite similar age-specific incidence rate patterns, the age distribution of adult ALL, and consequently the estimates of AYLL, can vary slightly across countries.

Utilization of the most recent data available from CI5 to estimate the international incidence of ALL is a notable strength of this analysis as is the provision of separate estimates of overall, childhood, and adult ALL incidence. In addition, this study projects the annual incidence of ALL in future years and is, to our knowledge, the first to estimate the average number of potential years of life lost to ALL, a valuable measure of the burden of this disease. Still, the conclusions drawn in the study are somewhat constrained by the limitations in the data available. For instance, given the lack of national cancer registries in many countries, the CI5 database is largely comprised of data from regional cancer registries that may only cover small subnational areas; it is possible that measures of cancer incidence in the regional registries included in CI5 do not always accurately reflect patterns of incidence in the entire country. Furthermore, given that ALL is a rare malignancy, the trends reported in regional registries with particularly low incidence rates warrant cautious interpretation as they are based on small numbers of diagnoses and are susceptible to random variation. The lack of mortality and survival data for countries other than the USA is another important limitation of this study. As such, to estimate mortality rates and AYLL for other countries, we relied on US age-specific ratios of incidence to mortality rates, which essentially assumes similar survival rates across countries. Thus, if the true survival rates in other countries differ greatly from those observed in the USA, we may have underestimated or overestimated mortality rates for some age groups and in turn underestimated or overestimated country-specific deaths and years of life lost from ALL. However, when we compared our estimated mortality rates with those from country-specific sources, we found little difference in regard to the age distribution of mortality or the estimation of AYLL. In addition, it is important to note that although accurate mortality rates are necessary to estimate the actual number of deaths and the total years of life lost, the estimation of AYLL is not dependent on the accuracy of these measures, but rather the distribution of the number of estimated deaths across age groups. Further, our estimates of 5-year relative survival among children and adults with ALL in the USA are similar to those from recent published survival estimates for ALL in Japan and European countries [25, 34, 57, 58]. Therefore, given similar patterns of incidence and survival across age groups for ALL, we believe that ratios of incidence to mortality rates from a single country such as the USA provide reasonable approximations of mortality rates in other countries solely for the purpose of estimating AYLL.

In summary, there is variation in the incidence of ALL by age and geographic region. However, age-standardized incidence estimates of ALL in our study only ranged from 1 to 2 per 100,000 people, whereas previous research [29] estimated a wider range of 1–4.75 per 100,000, perhaps suggesting that more recent data reflect greater consistency in the identification and reporting of ALL across nations since the WHO development of a consensus-based classification system for hematologic malignancies. In addition, despite long-term survival rates near 90 % among children, survival remains particularly poor in adults. The noted effect of older age on survival and the substantial AYLL among adults with ALL informs on the burden of this grievous disease and highlights the need to develop better treatments.

Compliance with ethical standards

The manuscript does not contain clinical studies, patient data, or research involving human participants or animals.

Conflict of interest A.J.K., V.M.C., and M.A.K. are employees of Amgen Inc. W.M.S. is an employee of Amgen Ltd.

Appendix

See Table 5.

Table 5 Comparison of country-specific and approximated mortality rates in the estimation of the number of deaths, total years of life lost, and average years of life lost from ALL in 2015

Country	Age group	Est. Population, 2015 (in 1000s)	Life expectancy	Country-specific ALL mortality rates[a]				Approximated ALL mortality rates			
				Mortality rate (per 100k)	No. deaths	PYLL	AYLL	Mortality rate (per 100k)	No. deaths	PYLL	AYLL
Australia	0–4	1604	82	0.29	5	381		0.44	7	576	
	5–9	1530	78	0.45	7	537		0.51	8	611	
	10–14	1450	73	0.38	6	402		0.49	7	520	
	15–19	1504	68	0.51	8	522		0.46	7	474	
	20–24	1608	63	0.44	7	446		0.55	9	561	
	25–29	1745	58	0.32	6	324		0.30	5	299	
	30–34	1746	53	0.34	6	315		0.30	5	279	
	35–39	1598	49	0.26	4	204		0.42	7	327	
	40–44	1658	44	0.29	5	212		0.31	5	230	
	45–49	1571	39	0.34	5	208		0.38	6	233	
	50–54	1576	34	0.51	8	273		0.60	10	323	
	55–59	1453	30	0.53	8	231		0.66	10	287	
	60–64	1296	25	0.49	6	159		0.78	10	252	
	65–69	1166	21	1.25	15	306		0.97	11	238	
	70–74	852	17	1.15	10	167		1.57	13	228	
	75–79	636	13	1.33	8	110		1.26	8	104	
	80–84	452	10	1.59	7	72		1.82	8	82	
	85+	477	7	2.56	12	85		1.24	6	42	
	0–19	6088			25	1842	74.5		29	2181	75.3
	20+	17,834			107	3111	29.0		113	3485	30.8
	Total	23,922			132	4953	37.5		142	5666	39.9
Denmark	0–4	320	79	0.37	1	94		0.39	1	99	
	5–9	328	75	0.23	1	57		0.45	1	111	
	10–14	332	70	0.17	1	40		0.35	1	82	
	15–19	351	65	0.46	2	105		0.41	1	93	
	20–24	366	60	0.40	1	88		0.67	2	148	
	25–29	344	55	0.29	1	55		0.19	1	36	
	30–34	319	50	0.26	1	41		0.26	1	41	
	35–39	352	46	0.24	1	39		0.26	1	41	
	40–44	390	41	0.25	1	40		0.22	1	36	
	45–49	407	36	0.22	1	32		0.43	2	64	
	50–54	399	31	0.22	1	27		0.30	1	37	

Table 5 continued

Country	Age group	Est. Population, 2015 (in 1000s)	Life expectancy	Country-specific ALL mortality rates[a]				Approximated ALL mortality rates			
				Mortality rate (per 100k)	No. deaths	PYLL	AYLL	Mortality rate (per 100k)	No. deaths	PYLL	AYLL
	55–59	358	27	0.36	1	35		0.53	2	51	
	60–64	339	23	0.31	1	24		0.50	2	39	
	65–69	347	19	0.33	1	22		0.39	1	26	
	70–74	280	15	1.24	3	52		0.97	3	41	
	75–79	187	12	1.13	2	25		1.73	3	39	
	80–84	122	9	0.67	1	7		0.56	1	6	
	85+	119	6	0.39	0	3		0.75	1	5	
	0–19	1331			4	295	71.5		5	385	72.2
	20+	4329			17	491	28.5		21	610	28.8
	Total	5660			21	785	36.8		26	995	37.6
Spain	0–4	2469	81	0.46	11	920		0.33	8	655	
	5–9	2542	78	0.63	16	1249		0.50	13	992	
	10–14	2313	73	0.68	16	1148		0.52	12	879	
	15–19	2114	68	0.57	12	819		0.47	10	682	
	20–24	2281	63	0.39	9	560		0.54	12	771	
	25–29	2627	58	0.30	8	457		0.25	7	383	
	30–34	3394	53	0.29	10	522		0.37	13	663	
	35–39	4083	48	0.31	13	608		0.32	13	630	
	40–44	3976	43	0.25	10	427		0.39	15	659	
	45–49	3760	38	0.38	14	543		0.45	17	637	
	50–54	3460	34	0.34	12	400		0.48	16	560	
	55–59	3011	29	0.38	11	332		0.53	16	463	
	60–64	2551	25	0.63	16	402		0.97	25	616	
	65–69	2370	21	0.67	16	333		1.08	26	536	
	70–74	1920	17	0.77	15	251		1.01	19	331	
	75–79	1594	13	1.03	16	213		1.25	20	259	
	80–84	1402	10	1.31	18	184		1.35	19	189	
	85+	1334	7	1.59	21	148		0.48	6	45	
	0–19	9438			55	4137	75.0		43	3207	74.8
	20+	37,763			189	5381	28.4		224	6743	30.1
	Total	47,201			245	9518	38.9		267	9951	37.3

Table 5 continued

Country	Age group	Est. Population, 2015 (in 1000s)	Life expectancy	Country-specific ALL mortality rates[a]				Approximated ALL mortality rates			
				Mortality rate (per 100k)	No. deaths	PYLL	AYLL	Mortality rate (per 100k)	No. deaths	PYLL	AYLL
UK	0–4	3869	80	0.28	11	867		0.35	14	1096	
	5–9	3920	76	0.26	10	775		0.42	16	1252	
	10–14	3461	71	0.26	9	639		0.37	13	912	
	15–19	3647	66	0.32	12	770		0.41	15	983	
	20–24	4018	61	0.37	15	907		0.46	19	1137	
	25–29	4335	57	0.24	10	593		0.21	9	523	
	30–34	4302	52	0.15	6	336		0.24	10	530	
	35–39	3942	47	0.16	6	296		0.23	9	427	
	40–44	4249	42	0.23	10	410		0.27	11	480	
	45–49	4650	37	0.23	11	396		0.30	14	516	
	50–54	4527	33	0.27	12	403		0.35	16	518	
	55–59	3916	28	0.46	18	504		0.47	18	514	
	60–64	3468	24	0.50	17	416		0.53	18	439	
	65–69	3593	20	0.67	24	481		0.74	26	528	
	70–74	2695	16	0.60	16	259		0.88	24	378	
	75–79	2145	12	1.06	23	273		1.00	21	258	
	80–84	1557	9	1.04	16	146		1.41	22	198	
	85+	1548	7	0.87	13	94		0.89	14	97	
	0–19	14,897			42	3050	73.2		58	4243	73.3
	20+	48,945			199	5515	27.8		232	6543	28.2
	Total	63,842			240	8565	35.6		290	10,786	37.2

PYLL potential years of life lost, *AYLL* average potential years of life lost

[a] Sources of country-specific mortality data: Australia, AIHW [48]; Denmark, NORDCAN [49]; Spain, Institute of National Statistics [47]; UK, Office of National Statistics and NHS National Services Scotland [45, 46]

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