Childhood cancer burden: a review of global estimates

Nickhill Bhakta, Lisa M Force, Claudia Allemani, Rifat Atun, Freddie Bray, Michel P Coleman, Eva Steliarova-Foucher, A Lindsay Frazier, Leslie L Robison, Carlos Rodriguez-Galindo, Christina Fitzmaurice

5-year net survival of children and adolescents diagnosed with cancer is approximately 80% in many high-income countries. This estimate is encouraging as it shows the substantial progress that has been made in the diagnosis and treatment of childhood cancer. Unfortunately, scarce data are available for low-income and middle-income countries (LMICs), where nearly 90% of children with cancer reside, suggesting that global survival estimates are substantially worse in these regions. As LMICs are undergoing a rapid epidemiological transition, with a shifting burden from infectious diseases to non-communicable diseases, cancer care for all ages has become a global focus. To improve outcomes for children and adolescents diagnosed with cancer worldwide, an accurate appraisal of the global burden of childhood cancer is a necessary first step. In this Review, we analyse four studies of the global cancer burden that included data for children and adolescents. Each study used various overlapping and non-overlapping statistical approaches and outcome metrics. Moreover, to provide guidance on improving future estimates of the childhood global cancer burden, we propose several recommendations to strengthen data collection and standardise analyses. Ultimately, these data could help stakeholders to develop plans for national and institutional cancer programmes, with the overall aim of helping to reduce the global burden of cancer in children and adolescents.

Introduction

Childhood cancer mortality rates were higher 50 years ago, but can now fortunately be successfully treated in approximately 80% of cases where there is access to modern treatments and robust, supportive care.[1] However, only 10% of the world's children live in high-income countries (HICs) where effective care is broadly accessible.[2,3] Over the past decade, the widening divide in cancer care and outcomes between HICs and the rest of the world has garnered important opportunities for prevention, treatment, and palliation.[4] Children with cancer, however, represent a small proportion (approximately 1%) of all cancers diagnosed worldwide each year, of which nearly all are not amenable to a defined prevention strategy. Unfortunately, children are often neglected in cancer control planning efforts, despite a disproportionately high number of person-years of life lost due to missed opportunities to diagnose and treat cancer in low-income and middle-income countries (LMICs).[5–7]

The magnitude of the global burden of childhood and adolescent cancer remains poorly quantified. There are no global estimates of incidence, survival, and mortality for children with cancer in most LMICs. Creating sound estimates of the global burden of childhood cancer is challenging because of the paucity of high-quality cancer registration and vital statistics data in LMICs, as well as the differences in the aetiology, pathogenesis, and presentation of the most common neoplasms between children and adults.

Up-to-date and accurate epidemiological data are essential to help prioritise health policy decisions, and to develop meaningful cancer control plans or strategies for individual nations. Effective planning for estimating resource needs (financing, health workforce, infrastructure, medicines, diagnostics, and health technologies) and for the organisation and delivery of health services depends on understanding how many children will develop and survive cancer, and on what types of cancers and long-term effects from cancer-directed treatment can be expected. To assess the available data on the global burden of cancer in children, we compared the data sources and methods of all major studies in children and adolescents (aged 0–19 years). We have also identified key requirements for complete and accurate burden estimates.

Data collection

Search strategy and selection criteria

To identify studies describing any element of the global childhood and adolescent cancer burden, we did a scoping review of the published literature using a modified PRISMA 2009 approach.[8,9] Rather than relying solely on expert knowledge, a decision was made to do a scoping review to ensure a thorough investigation of the literature was completed. Adaptations were based on scoping review guidelines and recommendations (search strategy available in the appendix, p 2).[10] Criteria for inclusion were studies that contained data of patients with cancer aged 20 years or younger; reported data for at least two of the ten most common malignancies in children based on the Surveillance, Epidemiology, and End Results programme rankings in the USA;[1] obtained primary data from population-based cancer registries or vital registration systems; described at least one of the following measures: incidence, survival, prevalence, or mortality; reported results from at least three WHO regions; and had been published between Jan 1, 2000, and Feb 1, 2018. Exclusion criteria were those publications that were not published in English; publications that were from the same research programme; or were review articles. As we assumed studies inclusive of data from multiple regions would require substantial global collaboration, the decision to include only English language publications was considered tenable. The databases we searched were PubMed, Medline via Web of Science, and SCOPUS. All abstracts identified by the search were reviewed for inclusion.

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Department of Global Pediatric Medicine (N Bhakta MD, Prof C Rodriguez-Galindo PhD), **Department of Epidemiology and Cancer Control** (N Bhakta, Prof L L Robison PhD), **Department of Oncology** (N Bhakta, L M Force MD, C Rodriguez-Galindo), **St Jude Children's Research Hospital, Memphis, TN, USA; Cancer Survival Group, Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK** (C Allemani PhD, Prof M P Coleman BM BCh); **Harvard T H Chan School of Public Health and Harvard Medical School, Harvard University, Boston, MA, USA** (Prof R Atun FRCP); **Section of Cancer Surveillance, International Agency for Research on Cancer, Lyon, France** (F Bray PhD, E Steliarova-Foucher PhD); **Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA** (A L Frazier MD); **and Division of Hematology, Department of Medicine** (C Fitzmaurice MD), **Institute for Health Metrics and Evaluation** (C Fitzmaurice), **University of Washington, Seattle, WA, USA**

Correspondence to:
Nickhill Bhakta, Department of Global Pediatric Medicine, St Jude Children's Research Hospital, Memphis, TN 38105, USA
nickhill.bhakta@stjude.org

See **Online** for appendix

	IICC-3[12]	GLOBOCAN 2012[13]	GBD 2016[26]	CONCORD-3[15]
Publication year	2017	2015	2017	2018
Years included in study	2001–10	2012	1990–2015	2000–14
Coordinating organisation	IARC	IARC	Institute for Health Metrics and Evaluation	Cancer Survival Group, London School of Hygiene and Tropical Medicine
Global estimates	Not applicable	Yes	Yes	Not applicable
Number of registries included	153	375	562	322
Proportion of registries in low-income and low-middle-income countries*	11%	7%	12%	5%
Countries or territories included	62	184	195	71
Subnational geographical estimates	No	No	Yes	Yes
Age strata (years)	0–4, 5–9, 10–14, 15-19	0–14	0–4, 5–9, 10–14, 15–19	0–14
Outcomes estimated	Incidence	Incidence, mortality	Incidence, prevalence, mortality, disability-adjusted life-years	5-year net survival
Classification†	ICCC-3	ICD-10 (selected sites and subsites)	ICD-9 and ICD-10	ICD-O-3
Cancers included	Leukaemias‡, lymphomas¶, CNS tumours, neuroblastoma, retinoblastoma, kidney, hepatic, bone, soft tissue sarcoma, germ cell tumours, epithelial tumors, other and unspecified	Leukaemias§, Hodgkin lymphoma, NHL, CNS, kidney§, liver§, Kaposi sarcoma	ALL, AML, Hodgkin, NHL, CNS, kidney§, liver§	Acute lymphoblastic leukaemia¶, lymphomas, CNS tumours
Uncategorised cancers (%)	0%	30%	29%	Not applicable
Annual estimate of the global number of incident cases in age range 0–19 years	Not applicable	163 284	240 942	Not applicable
Annual estimate of the global number of cancer deaths in age range 0–19 years	Not applicable	79 956	90 075	Not applicable

IARC=International Agency for Research on Cancer. ICCC-3=International Classification of Childhood Cancer, Third Edition. ICD-9=International Classification of Diseases, Ninth Revision. ICD-10=International Classification of Diseases, Tenth Revision. ICD-O-3=International Classification of Diseases for Oncology, Third Edition. ALL=acute lymphoblastic leukaemia. AML=acute myeloid leukaemia. NHL=non-Hodgkin lymphomas. *Low income and low-middle income country percentages calculated on the basis of World Bank fiscal Year 2018; upper-middle income countries not included in the proportions reported. †Cancer coding might differ between the original data and the categories according to which they are presented. ‡ALL and AML not estimated separately; §For kidney and liver categories, topographic codes were used in GLOBOCAN and Global Burden of Disease studies, and histology was used in IICC-3. ¶Leukaemias were further stratified into ALL and AML in a CONCORD-2 sub-analysis and in the open-access online data from IICC-3.

Table 1: **Comparison of available data on global paediatric cancer burden approaches**

Sources of data and methods

We reviewed a total of 987 abstracts. After evaluation, five major research programmes that have estimated the burden of cancer within the 0–19 age range in at least three of the six WHO regions were identified: International Incidence of Childhood Cancer (IICC-3),[11,12] GLOBOCAN 2012,[7] Global Burden of Disease Study (GBD) 2016,[13] CONCORD (CONCORD-3),[14] and SurvCan.[15] Out of the five programmes, all but SurvCan used the conventional age categories for children: 0–14 years for children and 0–19 years for adolescents. SurvCan included data on patients diagnosed during 1990–2001 in 14 countries in Africa, Asia, the Caribbean, and Central America, and there were 5 age ranges in most Survcan3 registry analyses. However, children and adolescents were included in the first broad age range that included young adults (younger than 45 years). Therefore, SurvCan estimates were excluded from this Review because it was impossible to determine childhood cancer survival alone from the data that was available.

Table 1 shows the differences in the methods applied, the main burden measures reported (incidence, survival, and mortality), and the differences in methods used between the selected studies. IICC-3 and CONCORD-3 showed observed data on cancer incidence and survival, respectively, from countries or regions covered by population-based cancer registries. GLOBOCAN 2012 and GBD 2016 used observed data and a range of sources as inputs to various statistical models to produce selected subnational, national, regional, and global cancer burden estimates.

Findings

Cancer incidence from IICC-3

The results and methods from the IICC-3 study[12] were published and made available open access in 2017; incidence of childhood and adolescent cancer was

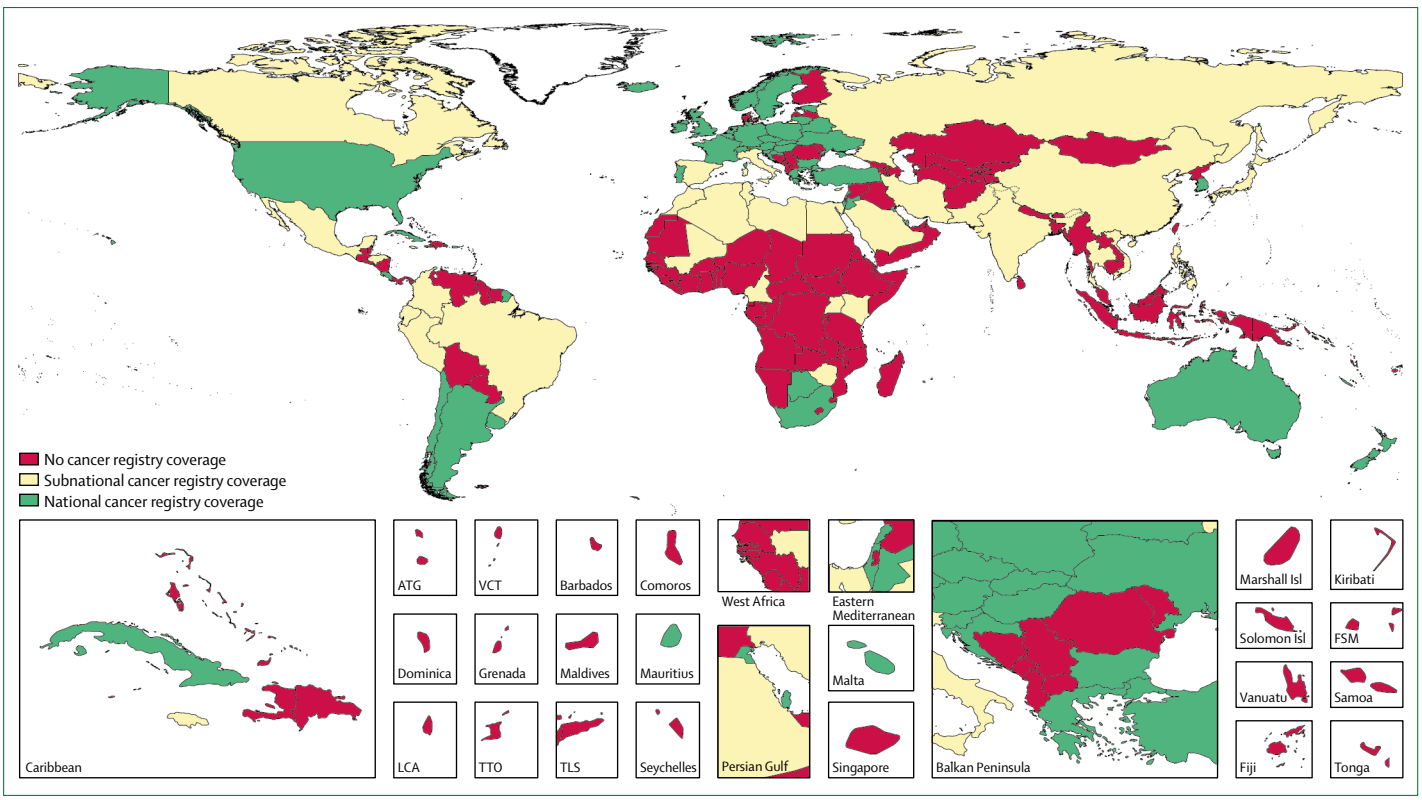


Figure 1: **Global cancer registration coverage of the childhood population (aged 0–14 years) based on the 308 registries contributing to the international incidence of childhood cancer study[11]**
ATG=Antigua and Barbuda. VCT=Saint Vincent and the Grenadines.

reported as age-specific and age-standardised incidence rates by sex and age groups (ie, 0–14 years and 15–19 years). Data were requested from all known population-based cancer registries but only included if they met a defined set of quality criteria, with 72% (308 out of 420) of submitted registry datasets meeting these standards. A subset of the available data, covering 2001–10, was used to provide pooled incidence rates, grouped into 19 strata by world regions and, when possible, ethnic groups.[11] IICC-3 is unique among the global studies of childhood cancer incidence in that individual patient data were collected from population-based cancer registries and that all the included cancer cases were classified and presented using the third edition of the International Classification of Childhood Cancer (ICCC-3).[16]

With scarce but high-quality data available through IICC-3, exploring the scope and objectives of the study showed some opportunities for future research. First, we put together a map of the coverage of national and subnational population-based cancer registries based on high-quality data that were included in the IICC-3 and that were made available as open access by the research programme (figure 1).[12] National and subnational coverage data for incidence was available from 308 registries. The map showed that a large proportion of LMICs in Africa and central and southeast Asia did not submit or produce high-quality cancer registration data for children with cancer. To get an accurate appraisal of the current and future disease burden in addition to ancestry-specific genomic determinants of childhood cancer risk, it will be essential to develop high-quality population-based registries in LMICs.[17–20] Second, the data reported were reflective of the patients registered in the participating registries. Although 11·4% of the global population of children was covered by registries included in the analysis for 2001–10,[11] the overall incidence was weighted towards those children observed in the well covered areas.

Survival estimates from CONCORD-3

CONCORD-3 is the only study on the global cancer burden to report cancer survival among children. It provided 5-year net survival estimates for children (aged 0–14 years) diagnosed with acute lymphoblastic leukaemia, lymphomas, and brain tumours during 2000–14 with complete summary tables by registry.[14] Additional data, including life tables and tools for analysis, are available on the CONCORD website. Although acute myeloid leukaemia was not included in CONCORD-3, a separate subanalysis done in 2017 using CONCORD-2 data, recently provided 5-year net survival estimates for both acute lymphoblastic leukaemia and acute myeloid leukaemia up to 2009.[21]

For more **information** see http://csg.lshtm.ac.uk/research/themes/concord-programme/

	GLOBOCAN 2012[13]	Global Burden of Disease 2016[26]
Data sources	Cancer incidence in five continents x, individual population-based cancer registries, WHO vital statistics, survival data	Cancer incidence in five continents v–x, individual population-based cancer registries, vital statistics (both WHO and national), verbal autopsies
Data quality criteria for inclusion	Same as in the data sources; method of estimation adapted to the quality of available data	None, GBD estimation methods correct for sampling and non-sampling errors
Incidence estimation	Estimates based on best available information from subnational and national population-based cancer registries and vital statistics of the index country or region	Based on modelled mortality estimates using separately modelled mortality-to-incidence ratios
Mortality estimation	Estimation from local, regional, pooled, and neighbour countries' mortality or from incidence estimates and survival	Cause of death ensemble models using mortality data inputs as well as cancer registry incidence inputs that have been transformed to mortality estimates using separately modelled mortality-to-incidence ratios; models use various covariables and constrain the sum of the cause-specific mortality rates to the total mortality from all causes combined
Uncertainty estimates	No	Yes
Key limitations of the cancer burden estimates for LMICs	Data presented according to ICD site codes, which do not reflect the major childhood cancer diagnostic groups, information from paediatric cancer registries was not considered	Data presented according to ICD site codes, which do not reflect the major childhood cancer diagnostic groups, information from paediatric cancer registries was not considered, adult mortality-to-incidence ratios were used to estimate childhood cancer incidence from childhood mortality data

***Table 2*: Differences between the methods for modelling incidence and mortality in GLOBOCAN 2012 and Global Burden of Disease Study 2016**

CONCORD-3 includes individual patient data from population-based cancer registries. Centralised data quality checks were performed, including the standard quality checks similar to those used in IICC-3 and quality checks specific for survival analysis. Summary quality control indicators were published for each cancer, country, registry, and calendar period.[14]

Similar to IICC-3, cancer data were submitted by registries using the third edition of the International Classification of Diseases for Oncology (ICD-O-3) for all or part of the 15-year period (2000–14). Age-standardised net survival, a measure of the probability of patients with cancer to survive their cancer after controlling for competing risks of death (background mortality), was estimated at 5 years after diagnosis by a cohort approach for patients diagnosed between 2000–04 and 2005–09, and by a period approach for patients diagnosed between 2010 and 2014, where less than 5 years of follow-up data were available.[22] To use net survival as a metric to account for the very wide variation in background mortality between populations and over time, life tables for all-cause mortality, by single calendar year, sex, age, and, where possible, race or socioeconomic status, were constructed for each population covered by any registry participating in CONCORD-3.[23] 5-year trends in survival were generated where data were available.

The gaps that remain after completion of the CONCORD-3 study are similar to those noted for IICC-3 (eg, the scarcity of high-quality cancer registration data from LMICs). Additionally, solid tumours, which represent approximately a third of childhood cancers in HICs, have not yet been included in the CONCORD programme. Finally, the observed survival among children in low-income and low-middle-income countries remains unknown because of the scarcity of quality data from population-based cancer registries in these settings.

GLOBOCAN and the GBD study (model-based approaches)

The estimation of national, regional, and global cancer burden has a long history and includes the studies done at the International Agency for Research on Cancer (IARC) since the 1980s as a prelude to the multiple GLOBOCAN editions and GBD estimates. Both GLOBOCAN and GBD estimated incidence, mortality, and prevalence of cancers for all countries, age groups, and both sexes covering the entire lifespan. The GBD study also produced estimates for cancers from 1990 to 2016 and also reported years lived with disability, years of life lost, and disability-adjusted life-years (DALYs), a metric that accounts for both the fatal and non-fatal components of disease burden.[6,24] A comparison of the different outcomes reported is available in table 1.

Data sources

Table 2 summarises the differences in GLOBOCAN and GBD source data and the analytic approaches used. For both studies, population-based cancer registry data and vital registration systems data were used.[25] The GBD study also included verbal autopsy data for selected cancers.[26] The data sources for GBD and GLOBOCAN included the published registry data from Cancer Incidence in Five Continents (CI5)[27] a series of monographs, produced by IARC and the International Association of Cancer Registries, with the objective to make comparable data on cancer incidence from a wide range of geographical locations, and other publicly available data sources. Both studies preferentially used all available data, rather than excluding data of that were of lesser quality, because they might have reflected incidence or mortality patterns to some extent. GLOBOCAN developed an alphanumeric scoring system to indicate the quality of available data for incidence and mortality and separated it by country.[28] The GBD study also used a rating system to describe the mortality data quality.[24] Finally, because of the complexity of the multiple statistical models used, the GBD 2016 report includes charts detailing fulfilment of and compliance with the GATHER guidelines.[29] Additionally, data sources used, descriptive flowcharts, and references to the corresponding statistical methods used to generate the estimates are included in the supplementary materials.[6]

	Number of cases			Number of deaths		
	GLOBOCAN 2012	GBD 2016 (UI)	Ratio*	GLOBOCAN 2012	GBD 2016(UI)	Ratio*
Leukaemias†	49 752	63 230 (57 517–67 989)	1·27	27 775	29 165 (26 846–32 673)	1·05
Acute lymphoblastic leukaemia	Not estimated	30 089 (28 217–33 082)	..	Not estimated	12 489 (11 429–14 828)	..
Acute myeloid leukaemia	Not estimated	11 631 (10 376–13 178)	..	Not estimated	5811 (5030–6840)	..
Brain and nervous system tumours	20 105	29 967 (27 612–32 022)	1·49	10 458	15 828 (14 066–17 532)	1·51
Neuroblastoma	Not estimated	Not estimated	..	Not estimated	Not estimated	..
Non-Hodgkin lymphoma	16 514	17 350 (14 722–18 746)	1·05	7223	10 974 (9195–12 375)	1·52
Kidney tumours (mostly Wilms' tumour)‡	9656	13 794 (12 988–14 437)	1·43	5547	2481 (2305–2654)	0·45
Bone tumours	Not estimated	Not estimated	..	Not estimated	Not estimated	..
Hodgkin lymphoma	6744	5220 (4270–5946)	0·77	1737	2 421 (1798– 3069)	1·39
Rhabdomyosarcoma	Not estimated	Not estimated	..	Not estimated	Not estimated	..
Retinoblastoma	Not estimated	Not estimated	..	Not estimated	Not estimated	..
Categorised cancers	114 202	133 672 (119 243–146 284)	1·17	57 861	62 503 (54 630–71 192)	1·08
All cancers in age 0–14 years	163 284	184 856 (171 441–191 140)	1·13	79 956	82 552 (77 182–88 092)	1·03
Uncategorised cancers§	49 082	51 184 (46 850–54 878)	1·04	22 095	20 048 (18 287–22 478)	0·91
Proportion uncategorised	0·3	0·28	..	0·28	0·24	..

Malignancy ranked based on SEER incidence ages 0–14 years; the order of malignancies in this table is ranked by the frequencies in data from SEER, where incidence is presumed to be complete and is structured specifically for childhood cancers. GBD 2016 provided estimates of incidence and mortality for 195 countries and GLOBOCAN 2012 for 184 countries, therefore only countries included in both studies were included in the totals and the ratios. All estimates reflect 2012 figures. GBD=Global Burden of Disease. UI=uncertainty interval. *Ratio based on the absolute global number of row-specific childhood cancers reported in GBD to GLOBOCAN. †GLOBOCAN 2012 does not differentiate leukaemia based on WHO type; GBD 2016 estimates "other leukaemias" in addition to acute lymphoblastic leukaemia and acute myeloid leukaemia. ‡Neither group estimates Wilms tumour as a separate entity; however, as Wilms tumours represent a substantial majority of childhood kidney cancers where reliable histopathology incidence data are available, kidney tumours in this age group were assumed to represent primarily Wilms' tumours. §Uncategorised: cases included under "other neoplasms" category.

Table 3: **Differences between GLOBOCAN and GBD study in the global estimates of new cases and deaths from cancer in children (0–14 years) in 2012, by ICD-10 topographic group**

Model-based approaches

The GLOBOCAN and the GBD studies both estimated incidence, mortality, and prevalence, but the methods applied to model these estimates differ substantially. For the GLOBOCAN study, a two-pronged stepwise approach was used to estimate both incidence and mortality.[7] For incidence estimates, country-level estimates were preferentially used when available. When country-wide population-based coverage was not available, a hierarchical approach was applied that incorporated regional data from mortality and mortality-incidence ratios, subnational registry data, neighbouring country or regional data, and all cancer data. Mortality estimates followed a similar step-wise approach with six different methods used. Data included country-level data when available, incidence estimates modelled about country-specific survival, or neighbouring country or regional data. A complete description of GLOBOCAN methods has been published.[28]

The GBD study group used a uniform approach to estimate mortality and incidence.[26,30] Cancer mortality was estimated in an ensemble modelling approach where different combinations of covariables and model types are used.[31] Data inputs used to estimate mortality from the mortality–incidence ratios included vital registration system data, verbal autopsy data, and cancer registry incidence data. Socio-demographic index, a summary measure of a location's income per capita, average educational attainment, and fertility rate, was used as the predictive covariate in the mortality–incidence ratio modelling to reflect a location's development status.[30] In the ensemble model, covariates are ranked on the basis of the strength of evidence for their causal connection. For example, hepatitis B prevalence in liver cancer was a level one covariate, and education was a level three. Individual mortality estimates in the GBD are adjusted to separately estimate all-cause mortality to ensure that the estimated number of deaths due to single causes does not exceed all-cause mortality. Incidence in the GBD is estimated by

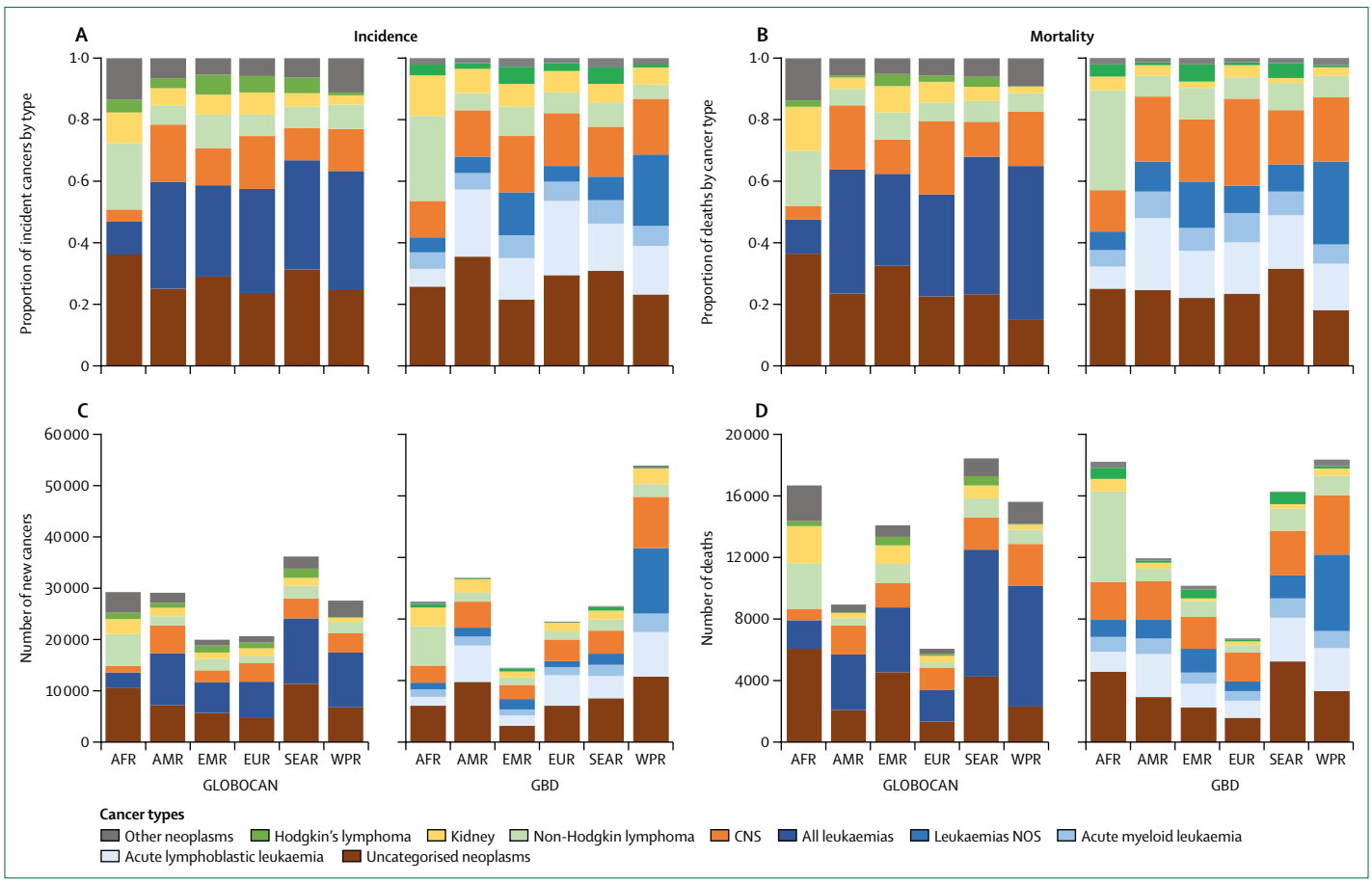


Figure 2*: Proportion and absolute number of cancer cases and deaths in children (aged 0–14 years) by type and WHO region

Figures 2A and 2C show incidence and figures 2B and 2D show mortality. AFR=Africa. AMR=Americas. EMR=Eastern Mediterranean. EUR=European. SEAR=Southeast Asia. WPR=Western Pacific Region. Leukaemia NOS=Leukaemia not otherwise specified. *Reference year 2012 data for GBD 2016 were used to compare estimates between studies.

using the separately modelled mortality–incidence ratio for each estimated cancer type, age group, sex, year, and location and dividing the mortality estimates by these mortality–incidence ratios.

Differences between GLOBOCAN and GBD results

For more on **GLOBOCAN** see http://globocan.iarc.fr/Pages/online.aspx

For more on **GBD** see http://ghdx.healthdata.org/gbd-results-tool

To compare differences between the estimates from GLOBOCAN and GBD, open-access data comprising national, regional, and global incidence and mortality data were downloaded from the online analysis portals maintained by both programmes (appendix 3). For GBD, the 2016 published estimates for the year 2012 were used for all data presented.[13] We used descriptive statistics to generate relative proportions by cancer type from the absolute incidence and mortality figures, and computed 95% confidence ellipses[32] from country level GLOBOCAN and GBD incidence and mortality rates using R version 3.4.3.

Estimates for the 2012 global annual incidence of all childhood cancers, ages 0–14 years, ranged from 163 284 cases per year from GLOBOCAN to 184 856 from GBD. Table 3 shows the incidence, mortality, and concordance of childhood cancer estimates from GLOBOCAN and GBD by topography and rank (ordered on the basis of incidence from the surveillance, epidemiology, and end results programme).[1] Nearly a third of childhood cancers in both studies remained uncategorised, meaning that these cancers were counted as part of an aggregated other cancer group in the GBD, or included in the total but not in the detailed cancer list in GLOBOCAN. Among the specific cancer groups, the GBD estimates were generally higher, although GLOBOCAN estimates were higher for Hodgkin's lymphoma and kidney cancers.

Figure 2 shows cancer incidence and mortality presented for the WHO world regions, as estimated by GLOBOCAN and GBD. The proportion of incident cancers and deaths by cancer type were similar for five of the six regions with the notable exception of the African region, where Kaposi's sarcomas (only available in the GLOBOCAN as GBD does not report Kaposi's Sarcoma incidence) and non-Hodgkin lymphomas are reported as more common. When the absolute numbers of new incident cases and deaths were compared, substantial inter-study regional variation was

observed. Results ranged from similar estimates in Europe to a nearly two times greater number of incident cancers as estimated by GBD in WHO's Western Pacific region compared with GLOBOCAN. Figure 3 shows the absolute number of overall incident cancer cases and cancer deaths but recategorised according to the 2012 World Bank income status (low income, low-middle income, upper-middle income, and high income). GLOBOCAN and GBD estimates were similar with the proportion of incident cases occurring in LMICs being 83·3% in the GLOBOCAN study and 82·1% in the GBD study with the proportion of deaths occurring in LMICs being 93·9% in the GLOBOCAN study and 93·5% in the GBD study. When incidence and mortality data were separated into the four main World Bank categories, the estimated childhood cancer incidence among upper middle-income countries was different. The main driver for the observed discordance observed in figure 2A, 2C (WHO's Western Pacific region), and 3A appear to stem from differences in estimates from China, where GLOBOCAN estimated there were 17 594 new cases of childhood cancer in 2012 compared with the GBD estimate of 43 187 new cases (appendix 6). Although it is unclear why there is such a different in results, the types of data analysis methods used might explain this difference.

Figure 4 shows the concordance between GLOBOCAN and GBD incidence and mortality for all childhood cancers combined, by country and World Bank income categories, which classify countries as low, low-middle, upper-middle, and high income.[33] The mean of the national childhood cancer incidence and mortality rates for countries within each World Bank income group are broadly concordant. At the country level, however, the size of the 95% confidence ellipses underscores the wide discordance between the two model-based approaches to estimating the burden of childhood cancer for ages 0–14 years. The concordance of both studies is illustrated in figure 4A, which shows that higher incidence rates were estimated for HIC and that the mean incidence rates for low-income countries and low-middle income countries were lower and fell outside the confidence ellipse for HIC. In figure 4B, the LMIC rates for all three categories appear to cluster and HICs have a lower mortality rate compared with the other categories, although the mean remains within all three LMIC confidence ellipses.

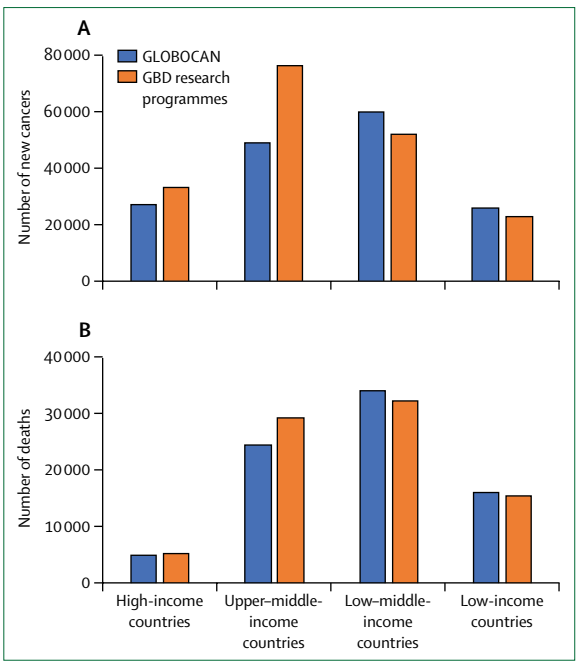


Figure 3: **Absolute number of overall cancer incidence (A) and mortality (B) cases in children (aged 0–14 years) by 2012 World Bank low-income and middle-income status***

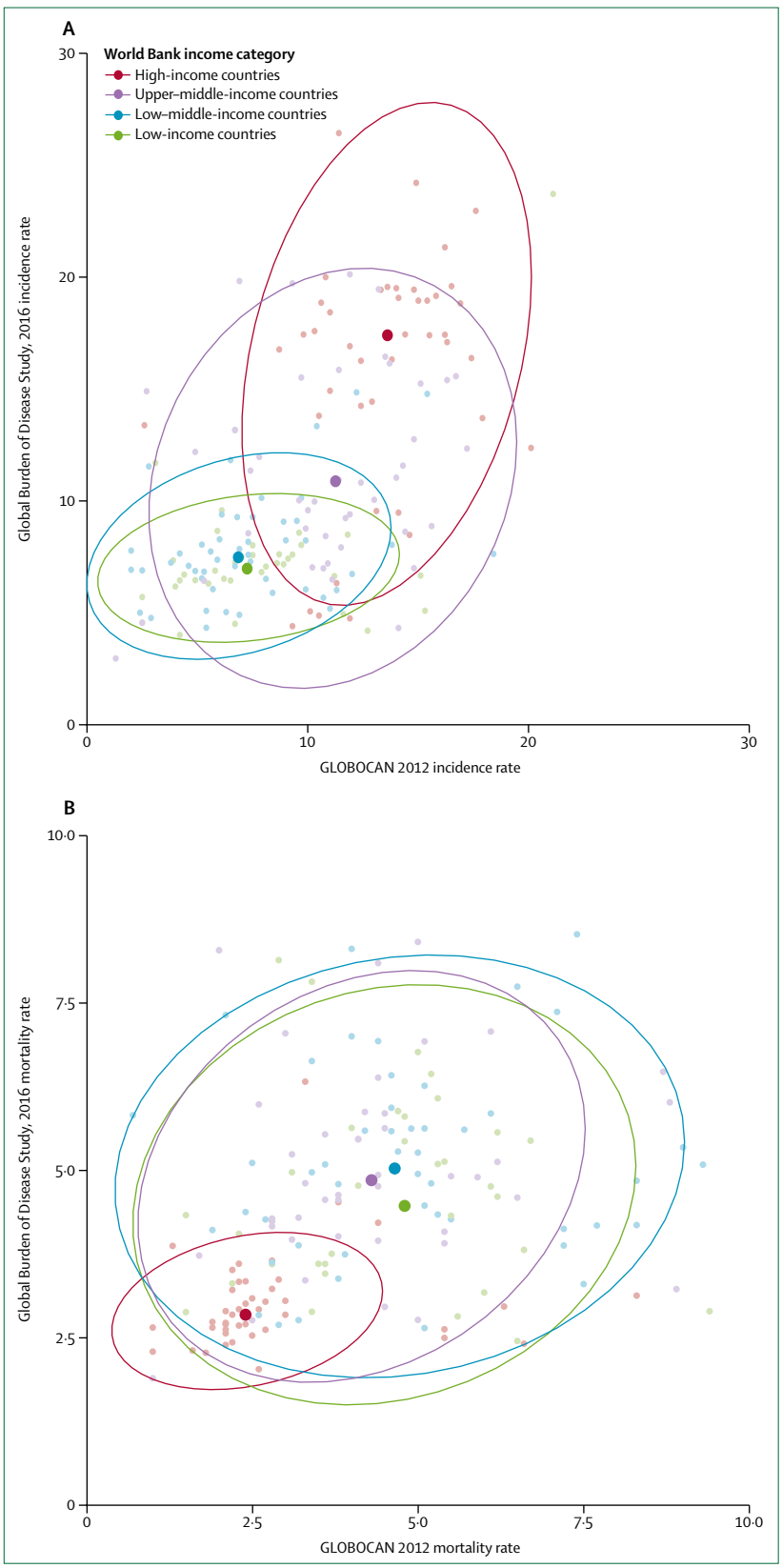
*Reference year 2012 data for GBD 2016 were used to compare estimates between studies.

Cautions in using model-based approaches to estimate childhood cancer burden

The GBD and GLOBOCAN burden estimates are routinely cited as authoritative, but they should be used cautiously when applied to cancers among children because of important methodological limitations affecting paediatric cancer burden estimation. First, both studies share an important gap with respect to paediatric cancer epidemiology: nearly a third of these cancers are not individually estimated by either group. A third of childhood cancers are uncategorised because the selection of ICD categories is based on the primary site of the cancer and not on histology to present the data. Although topography-based ICD cancer codes are appropriate to present most of the cancer burden in the total population, it is not adapted to appropriately characterise cancer among children. Cancers in children and adults are histologically, biologically, and epidemiologically distinct, therefore use of the ICCC-3 classification system would be more appropriate when estimating the burden among younger patients. Such a shift would also allow for a more applicable selection of covariates given the paucity of described environmental risk factors for childhood cancer.

Perhaps the most obvious example, for which specific approaches to estimation of the childhood and adolescent cancer burden would be most beneficial, is with the types of cancers estimated and how they are classified. The major difference with respect to classification between the two studies is that the country-level estimates available from GLOBOCAN aggregate all leukaemias, whereas GBD provides separate estimates for acute lymphoblastic leukaemia, acute myeloid leukaemia, and chronic myeloid leukaemia. A sub-analysis of leukaemia subtypes using GLOBOCAN and CI5 data provides global trends and proportions of leukaemia subtypes for children aged 0–14 years in 54 countries.[34] However, modelled data with country-specific estimates were not included in the analysis.

In terms of estimation approaches, neither study effectively describes the burden of extracranial solid



tumours in children. GLOBOCAN and GBD both produce estimates of cancer incidence and mortality on the basis of topographic codes for children aged 0–14, so the frequency of childhood cancers with very specific morphology, such as Wilms' tumour and hepatoblastoma, must be inferred on the basis of age and organ of origin, such as kidney or liver cancer. Furthermore, neither study estimates the incidence or mortality of neuroblastoma, osteosarcoma, Ewing's sarcoma, or retinoblastoma, but instead places them into the other cancer group. Taken together, extracranial solid tumours represent 17% of childhood cancers in HIC and they probably account for a large proportion of the uncategorised childhood cancers that are listed in table 1. This observation is particularly relevant because of the growing body of genetic predisposition data and observed variations in the global incidence of solid tumours among children.[19,35] Additionally, although years lived with disability and DALYs are estimated in the GBD study, these estimates have not taken into account the specific long-term treatment associated with chronic health conditions that occur in childhood cancer survivors.[36–38] Finally, GBD categorises all paediatric data, inclusive of the adolescent group, into 5-year age groups, but GLOBOCAN provides estimates for broad age groups of 0–14, 15–39, 40–44 years, and so forth, focusing on the age groups with the largest cancer burden. An article[39] focusing on the global burden of cancer among adolescents and young adults used GLOBOCAN methods and has reported global incidence and mortality outcomes for the 20–39 year age group.

Beyond differences in data preparation and modelling methods, a key gap in both burden estimates that has no obvious solution but remains an essential omission, is how to estimate the expected number of children who develop cancer globally each year. In countries with registries where access to complex diagnostics is limited, misdiagnosis and missed diagnoses might underestimate the true cancer burden. This underestimation is particularly important when interpreting GLOBOCAN estimates as they reflect the true diagnosed cancers. GBD attempts to quantify the total underlying burden diagnosed and undiagnosed by adjusting for so-called

Figure 4: **Overall childhood incidence (A) and mortality (B) rates in children (aged 0–14 years)***

Dark shaded dots correspond to the median GLOBOCAN 2012 (x-axis) and Global Burden of Disease Study 2016 (y-axis) rates for incidence (A) and mortality (B) by countries categorised using the World Bank income groupings. Lighter shaded dots correspond to country-specific incidence (A) and mortality (B) rates, age-standardised per 100 000 children 0–14 years. 95% confidence ellipses correspond to the income group by colour. Income groupings are based on the World Bank fiscal year 2018. HIC=high-income country. UMIC=upper-middle income country. LMIC=lower-middle income country. LIC=low-income country. All estimates based on incidence and mortality rates for the year 2012. Mauritius was excluded from the final figures and median calculations because of reported outlier rates but data is included in the appendix. *Reference year 2012 data for GBD 2016 were used to compare estimates between studies.

garbage codes, which are causes of death that should not be coded as the underlying cause of death, or undefined codes like ICD-10's code R99 (ill-defined and unknown cause of mortality). However, even this method has limitations as it is likely that some deaths due to childhood cancer are miscoded as infectious, especially in limited-resource settings. Estimating this effect is not a simple issue to remedy but will hopefully improve with better data by increasing diagnostic capacity and access to care, and with the validation of additional covariates when modelling paediatric cancer incidence.

An appreciation of all these limitations is essential when interpreting childhood cancer burden estimates. For example, an examination of the mean rates of incidence by income category in figure 4A suggests a correlation between increasing income status and cancer incidence. At face value, this would suggest children in lower income countries are at lower risk of developing cancer than their higher income counterparts. Attempts to explain this trend have suggested that global variations in mortality under the age of 5 years and inherited genetic predispositions to cancer are likely to be the cause.[2] However, if the reported data are due to underdiagnoses, with likely misidentified or never identified new cases or deaths, the interpretation could change and challenge how the global pediatric oncology community has traditionally understood regional variations in childhood cancer. Therefore, investigators should not assume that the available estimates reflect the true incidence of childhood cancer in LMICs. Rather, these data should be interpreted as the number of cases of childhood cancer being identified and seeking treatment within the health system, which is still an important finding with practical health-services planning implications.

Recommendations to improve estimation methods for the global childhood cancer burden

The objectives and methods in the four described studies differ in important ways. Although the IICC-3, CONCORD-3, GLOBOCAN, and GBD studies represent the four most comprehensive sources for estimates of childhood cancer incidence, survival, and mortality, a complete set of global data is unavailable. Over the past decade, several articles have used the GLOBOCAN data in particular to emphasise the global burden of childhood cancer in the absence of adapted sources.[2,40,41] However, a need to compare or appraise the methods used and propose improvements in the estimation approaches used is clearly needed.

The panel presents a list of proposed steps and initiatives as recommended by us to improve paediatric cancer burden estimates. These recommendations do not represent a formal consensus statement but were developed through several rounds of iterative input and agreement from all co-authors. Fundamental to robust estimates is high-quality observed data from population-based general or paediatric cancer registries that can represent the basis of evidence-based childhood cancer control plans. Given the paucity of quality-assured incidence data in LMICs, technical assistance for governments is needed to enable generation and use of their own data, including national estimates derived from these data sources and timely application of best practices to improve the quality of reported registry data (eg, reporting delay adjustments).[42] There is a great need for a multi-stakeholder action plan that emphasises the use of observed data by increasing the capacity of childhood cancer registries in LMICs to inform dedicated childhood cancer control plans. The Global Initiative for Cancer Registration Development, led by IARC with multiple global partners, represents an example of such an initiative.

Incorporating childhood cancer into the global prioritisation framework and developing more high-quality population-based cancer registries is an essential long-term investment, although the short-term step to

Fore more on the **Global Initiative for Cancer Registration Development** see http://gicr.iarc.fr

***Panel:* Recommendations from authors to improve estimates of the childhood cancer burden**

- Support existing cancer registries to improve the quality of childhood and adolescent International Classification of Diseases for Oncology data collected through quality control and quality assurance measures specific to the unique characteristics of cancer in younger patients
- Increase and improve follow-up of patients with cancer, so that survival and its determinants, including treatment abandonment can be measured
- Use observed incidence and survival data from cancer registries as baseline for estimates where possible
- Formulate frameworks and standards to encourage timely data sharing between hospital-based and population-based cancer registries on national level and global burden estimation groups on an international level
- Promote international data sharing for public health benefits while ensuring personal privacy rights
- Develop models, using appropriate classification approaches, to forecast the expected changes in cancer incidence among children on the basis of demographic shifts, potential reductions in non-communicable disease and diagnostic capabilities
- Develop statistical approaches to integrate data from large cancer survivorship studies to include cancer treatment related chronic health conditions when estimating disability-adjusted life-years
- Develop and disseminate technical guidelines that are specific for childhood cancer registration, including recommendations for collection of data on staging (aligned with Toronto consensus guidelines) and treatment (abandonment, modalities, and palliation)
- Ensure timely mapping between ICD-O and ICCC systems by taking into consideration pathological and clinical characteristics as well as continuity across time when defining classes and subclasses for analysis and reporting
- Create and disseminate cancer registration training curricula and opportunities that are specific for childhood cancer
- Use cancer categories that are relevant for childhood cancers and clinically meaningful for both observed and modelled data, and report outcomes using the third edition of the International Classification of Childhood Cancer groupings; results should be reported separately for the subgroups of leukaemia and lymphoma and CNS tumours should be reported by grading; reports should include results for major solid tumours common in childhood age

improve estimates should involve the use of adapted cancer categories such as the ICCC whenever ICD-O-3 data is available.[16] Because of the small numbers, many childhood cancers are grouped into broad categories that are not clinically meaningful. For example, leukaemias, lymphomas, CNS tumours, and other heterogeneous tumour subgroups should be defined by a common standard (currently ICCC-3) and categorised into subgroups that are relevant from a public health and clinical perspective. The most obvious example in which this requirement is relevant is when overview studies collapse acute lymphocytic leukaemia and acute myeloid leukaemia into a single leukaemia category. Although these two diagnoses are often grouped together, because of historic convention and the low incidence of acute lymphocytic compared with acute myeloid leukaemia in the adult population, they are different cancers with a substantial burden among children, and therefore should be reported separately for health-planning purposes. However, simply applying all 48 ICCC-3 categories to eliminate the proportion of uncategorised cancers noted in the GLOBOCAN and GBD studies is not a viable solution given the small numbers of childhood cancers and the large number of different rare cancer pathologies. Therefore, careful appraisal of how categories are grouped, particularly for the unspecified and other specified neoplasms, is an important action that should be taken and justified by each overview study.

Re-examination of the adapted cancer categorisation systems themselves, such as ICCC-3, is also needed. For example, lymphoblastic lymphomas are is classified with other non-Hodgkin lymphomas on the basis of historic convention, but it would be better categorised with acute lymphoblastic leukaemia, because of the similar biology and treatment. Similarly, segregating embryonal tumours, low-grade gliomas, and high-grade gliomas as distinct CNS categories is important given the required health services and expected clinical outcomes associated with each. These recommendations would not require substantial effort, because the ICD-O-3 classification system already makes these classification categories feasible.

Moreover, without access to multidisciplinary treatments, including cytotoxic chemotherapies, radiotherapy, surgery, and high-quality supportive care, childhood cancer is a fatal disease. Therefore, incidence data, although necessary for health services planning, need to be paired with access and outcomes data when contextualising the disease burden. Yet, high-quality childhood cancer registries and vital registration systems data remains the biggest impediment to accurate estimation of the childhood cancer burden.

Finally, although estimates of the cancer burden derived from models cannot replace observed data, they can help galvanise interest and advocate the need for observed data with wider coverage and higher quality. In assessing the current state and future evolution of the childhood cancer burden, it would also be important to include variables such as disease stage at diagnosis, abandonment of treatment, and follow-up of all registered patients for their vital status. The definition of internationally acceptable standards, such as the Toronto guidelines[43] for childhood cancers staging, represents a promising movement in this direction. Finally, creation of cancer registration training curricula that are specific for childhood cancer, at a level suitable for registrars and data entry specialists, represents an important remaining need in the field.[44]

Policy implications

With the advent of the Sustainable Development Goals[45] and the global drive towards universal health coverage by 2030, the World Health Assembly adopted the global cancer challenge resolution in May, 2017, an important event that added cancer prevention and control initiatives for all age ranges to the global action plan for the prevention and control of non-communicable diseases 2013–20.[46] As a first step towards developing action plans to address disparities in cancer control both locally and globally, a better understanding and appreciation of the differences and gaps in global childhood cancer burden estimates is an important prerequisite. For countries where population-based cancer registries exist, the observed data from these sources might be sufficient to guide efforts. However, among countries not covered by a participating registry in the IICC-3 or CONCORD-3 studies, the GLOBOCAN or GBD estimates of incidence, mortality, and adjusted life-years are potentially the only data available. The variability of the estimates, shown in figure 4, should serve as an incentive to establish suitable surveillance systems in each country.

Although several studies have recently shown that childhood cancer treatment is cost-effective,[47] affordability and financial toxicity (ie, problems a patient with cancer has related to the cost and subsequent sequalae associated with treatment) are also known barriers to successful paediatric cancer control initiatives that require policy interventions.[48,49] The private sector has provided a great amount of funding to support childhood cancer treatment programmes in LMICs.[50,51] If organisations were armed with accurate historic and current burden statistics, presented in an accessible and visually intuitive manner, they could leverage these data to improve education initiatives and increase fundraising efforts by showing real or potential impact to donors. Country case-examples suggest governments can also be swayed to increase access to care by disease burden metrics. For example, in response to a 2009 clinical study[52] that reported the survival and costs associated with treating children with acute lymphoblastic leukaemia, the Chinese Ministry of Health decided in 2010 to provide governmental funding to treat all children with the disease.

Conclusion

Cancers in children and adolescents are fundamentally different from the cancers seen in adults. To improve the relevance and quality of information on childhood cancer burden, data collection and analytic approaches that are specific for children and adolescents, not tied to the methods used to estimate the adult cancer burden, are required. This proposed approach to delink adult and paediatric cancer estimates would allow for additional flexibility and innovation. Some improvements to the measurement of the disease burden could be implemented quickly, but structural changes will require both time and new financial resources. These changes include expanding the coverage of childhood cancer registration, especially in LMICs; enhancing the quality of data collection through capacity-building and standardised data dictionaries; and development of training curricula for tumour registrars that are specifically tailored to the registration of cancers in children and adolescents.

A patchwork of estimates of the global burden of childhood and adolescent cancer is available, but they are either based on data covering only about a tenth of the world childhood population or are not adapted for this age range. Therefore, the results from these sources are highly heterogeneous. Because of the substantial differences between the estimates, making confident decisions on health policy, priority setting, cancer control strategy, and financing that is based on the available information is a challenging prospect.

Contributors

NB and CF developed the idea. NB, LMF, and CF drafted the Review and prepared the tables and figures. NB and LMF completed the scoping review. All authors contributed to interpretation of the findings, editing the article, and approved the final submitted version.

Declaration of interests

ALF is on the clinical adviser board of Decibel Therapeutics. The other authors declare no competing interests.

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