How many children are diagnosed with and survive cancer worldwide? A review of global estimates of the cancer burden in children

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Abstract

Among children and adolescents diagnosed with cancer today in many high-income countries, 5-year net survival is approximately 80%. This is encouraging as it shows what is possible. Unfortunately, the limited available data from low- and middle-income countries (LMIC), where nearly 90% of children with cancer live, suggest global survival is substantially worse. As LMIC are undergoing rapid epidemiological transition, with a shifting burden from infectious 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 study, we reviewed four worldwide studies of the global cancer burden that included data on children and adolescents. Each study used a variety of overlapping and nonoverlapping statistical approaches and outcome metrics. Moreover, to provide guidance with the aim of improving future estimates of childhood global cancer burden, we also propose several recommendations to strengthen data collection and standardize analyses. Ultimately, these data may aid stakeholders in developing plans for national and institutional program development, with the overall aim of helping to reduce the global burden of cancer in children and adolescents.

Background

Virtually fatal 50 years ago, cancer in children can now be successfully treated in approximately 80% of cases where there is ready access to modern treatments and robust supportive care.(1) However, only 10% of the world's children live in the high-income countries (HIC) where effective care is broadly accessible.(2, 3) Over the past decade, the widening divide in cancer care and outcomes between HIC and the rest of the world has garnered significant attention, especially for adult cancers where both prevention and early intervention represent viable, cost-effective opportunities to prevent, treat and palliate cancer.(4) Children with cancer, however, represent a small proportion (around 1%) of all cancers diagnosed worldwide each year, nearly all of which are currently 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- and middle-income countries (LMIC).(5-7)

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

Up-to-date and accurate epidemiologic data are critical for prioritization and health policy decisions, and in developing meaningful national cancer control plans or strategies. Effective planning for estimating resource needs (financing, health workforce, infrastructure, medicines, diagnostics and health technologies) and in the organization and delivery of health services, depends on understanding how many children will develop and survive cancer, and 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 methodology of all major studies in children and adolescents (ages 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 global childhood and adolescent cancer burden, we conducted 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 conduct a scoping review in order 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 page 2).(10) Inclusion and exclusion criteria were developed in advance of the search. Criteria for inclusion were

that studies: contained data on cancer patients up to 20 years of age; reported data for at least two of the ten most common malignancies in children based on Surveillance, Epidemiology and End Results Program (SEER) rankings in the United States(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 World Health Organization (WHO) regions; and publication was between January 2000 and February 2018. Criteria for exclusion publications in non-English, from the same research program, or were review articles. As we assumed studies inclusive of data from multiple regions would require significant global collaboration, the decision to include only English language publications was considered tenable. Databases searched were PubMed, Medline via Web of Science, and SCOPUS. All abstracts identified by the search were reviewed for inclusion.

Sources of data used

A total of 987 abstracts were reviewed. After evaluation, five major research programs that have estimated the burden of cancer within the 0-19 year age-range in at least three WHO regions were identified: International Incidence of Childhood Cancer (IICC-3)(11, 12), GLOBOCAN (2012)(13), Global Burden of Disease (GBD 2016)(14), CONCORD (CONCORD-3)(15), and SurvCan.(16) Among the five programs, all but SurvCan used the conventional age categories for children (0-14 years) or children and adolescents (0-19 years). SurvCan included data on patients diagnosed during 1990-2001 in 14 countries in Africa, Asia, the Caribbean and Central America, but children and adolescents were included in a broad age range with young adults (< 45 years old). Thus, as it was impossible to determine childhood cancer survival from the published data, SurvCan was excluded from this review.

Approaches used

Table 1 highlights the methods applied, the main burden measures reported (incidence, survival, and mortality) and the differences in methodology between the selected studies. IICC-3 and CONCORD-3 reported 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 (GBD only), national, regional and global cancer burden estimates.

Findings

Incidence measures from IICC-3

The results and methods from the IICC-3 study were published and made available as open-access online in 2017; childhood and adolescent cancer incidence were reported as age-specific and age-standardized incidence rates by sex and age groups (i.e., ages 0-14 years and 15-19 years).(12) Data were requested from all known population-based

cancer registries but only included if they met a defined set of quality criteria, with 72% (308/420) of submitted registry datasets meeting these standards. A subset of the available data, covering the entire period from 2001-2010, 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).(17)

With the limited but high-quality data available through IICC-3, exploring the scope and objectives of the study highlights some opportunities for future research. First, we show a map of the national and sub-national population-based cancer registry coverage based on high-quality data included in the IICC-3 and that were made available as open-access online by the research program (Figure 1).(12) National and subnational coverage data for incidence was available through 308 registries. The map shows that a large proportion of LMIC countries in Africa and central and south-east Asia either did not submit or produce high-quality cancer registration data for children with cancer. To obtain an accurate appraisal of the current and future disease burden in addition to ancestry-specific genomic determinants of childhood cancer risk, it will be critical to develop more high-quality population-based registries in LMIC.(18-21) Second, the data reported are 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 2001-2010,(11) the overall incidence were weighted towards those observed in the well covered areas.

Survival estimates from CONCORD-3

CONCORD-3 is the only study of the global cancer burden to report cancer survival among children. It provided five-year net survival estimates for children (0-14 years) diagnosed with ALL, lymphomas and brain tumors during 2000-2014 with complete summary tables by registry available in the supplementary appendix to the publication.(15) Additional data including life tables and tools for analysis are included on the CONCORD website.(22) Although AML was not included in CONCORD-3, a separate sub-analysis using CONCORD-2 data recently provided five-year net survival estimates for both ALL and AML up to 2009.(23)

CONCORD-3 includes individual patient data from population-based cancer registries. Centralized 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.(15)

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 2000-2014. Age-standardized net survival, a measure of the probability of cancer patients to survive their cancer after controlling for competing risks of death

(background mortality), was estimated at five 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 2010-14, where less than five years of follow-up data were available.(24) In order 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 socio-economic status, were constructed for each population covered by any registry participating in CONCORD-3.(25) Five-year trends in survival were generated where data was available.

The gaps that remain after completion of the CONCORD-3 study are similar to those noted for IICC-3. Additionally, solid tumors, which represent approximately one-third of childhood cancers in HIC, have not yet been included in the CONCORD program. Finally, the observed survival among children in low and low-middle income countries remains unknown due to the lack of quality data from population-based cancer registries in these settings.

GLOBOCAN and the Global Burden of Disease study (model-based approaches to the estimation of the global cancer burden in children and adolescents)

Estimating national, regional, and global cancer burden has a long history and includes the studies conducted at 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 life-span. The GBD study also produced estimates for cancers from 1990 to 2016 and also reported person-years lived with disability, person-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, 26) A comparison of the different outcomes reported is available in Table 1.

Data sources

The differences in GLOBOCAN and GBD source data and analytic approach are summarized in Table 2. For both studies, population-based cancer registry data and vital registration systems data were used.(27) The GBD study also included verbal autopsy data for selected cancers.(28) The data sources for GBD and GLOBOCAN included the published registry data from Cancer Incidence in Five Continents (CI5),(29) a series of monographs, produced by IARC and the International Association of Cancer Registries, with the objective to make available 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 lesser quality data, because the lesser-quality data may 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 separately by country.(13) The GBD also used a rating system to describe the mortality data quality.(26) Finally, given the complexity of the multiple statistical models used, the 2016 GBD cancer burden report includes charts detailing fulfillment of and compliance with the GATHER guidelines.(30)

In addition, data sources used, descriptive flowcharts and references to the corresponding statistical methods used to generate the estimates are included in the supplementary materials.(6)

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 rates 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-to-incidence ratios (MIR), sub-national registry data, neighboring country or regional data and "all cancer" rates. Mortality estimates followed a similar step-wise approach with six different methods used. Data included country-level rates when available, incidence estimates modeled on country-specific survival, or neighboring country/regional data. A complete description of GLOBOCAN methods has been published.(13)

The GBD study group used a uniform approach to mortality and incidence estimation.(28, 31) Cancer mortality was estimated in an ensemble modeling approach where different combinations of covariables and model types are used.(32) Data inputs used to estimate mortality from the MIR included vital registration system data, verbal autopsy data and cancer registry incidence data. Socio-demographic index (SDI), a summary measure of a location's income-per-capita, average educational attainment, and fertility rate, was used as the predictive covariate in the MIR modeling to reflect a location's development status.(31) In the ensemble model, covariates are ranked based on the strength of evidence for their causal connection. Hepatitis B prevalence in liver cancer for example, was a level one covariate, whereas 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 the all-cause mortality. Incidence in the GBD is estimated by using again the separately modeled MIR for each estimated cancer type, age group, sex, year and location and dividing the mortality estimates by these MIR.

Differences between GLOBOCAN and GBD results

To compare differences between the estimates from GLOBOCAN(33) and GBD(34), open-access data comprising national, regional and global incidence and mortality data were downloaded from the online analysis portals maintained by both programs (appendix page 3). For GBD, the 2016 published estimates for the year 2012 were used for all data presented.(14) Descriptive statistics were used to generate relative proportions by cancer type from the absolute incidence and mortality figures, and 95% confidence ellipses(35) were computed 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 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 based on the incidence from SEER).(1) Nearly one-third of childhood cancers in both studies remained uncategorized, meaning 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 are generally higher, although GLOBOCAN estimates were higher for Hodgkin lymphoma and kidney cancers.

In Figure 2, cancer incidence and mortality are 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) and non-Hodgkin lymphomas are reported as more common. When the absolute numbers of new incident cases and deaths are compared, substantial inter-study regional variation is observed. Results range from similar estimates in Europe to a nearly two-fold greater number of incident new cancers as estimated by GBD in the WHO Western Pacific region compared to GLOBOCAN. Figure 3 displays the absolute number of overall incident cancer cases and cancer deaths but recategorized according to 2012 World Bank Income Status (low-income, low middle-income, upper middle-income and high income). When categorized as all LMIC groups vs HIC, GLOBOCAN and GBD estimates are similar with 82.1% and 83.3% of incident cases and 93.5% and 93.9% of deaths occurring in LMIC, respectively.

Figure 4 displays the concordance between GLOBOCAN and GBD incidence and mortality rates for all childhood cancers combined, by country and World Bank income categories, which classify countries as low, low-middle, upper-middle and high-income.(36) 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 panel A, 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 panel B, the LMIC rates for all three categories appear to cluster while HICs have a lower mortality rate compared to the other categories, though the mean remains within all three LMIC confidence ellipses.

Cautions in using both model-based approaches as related to childhood cancer burden estimation

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 pediatric cancer burden estimation. First, both studies share an important gap with respect to pediatric cancer epidemiology: nearly one-third of

these cancers are not individually estimated by either group. This is due to the selection of ICD categories, based on cancer primary site and not histology, to present the data. While topography-based ICD cancer codes are appropriate to present the bulk of cancer burden in the total population, it is not adapted to appropriately characterize cancer among children. Cancers in children and adults are histologically, biologically and epidemiologically distinct, so 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 leukemias while GBD provides separate estimates for ALL, AML, and chronic myeloid leukemia (CML). A sub-analysis of leukemia subtypes using GLOBOCAN and CI5 data provides global trends and proportions of leukemia subtypes for children ages 0-14 in 54 countries.(37) However, modeled data with country-specific estimates were not included in the analysis.

In terms of estimation approaches, neither study effectively describes the burden of extra-cranial solid tumors in children. GLOBOCAN and GBD both produce estimates of cancer incidence and mortality on the basis of topographic codes for children ages 0-14 years, so the frequency of childhood cancers with very specific morphology, such as Wilms' tumor and hepatoblastoma, must be inferred based on age and organ of origin such as "kidney" or "liver" cancer. Furthermore, neither study estimates the incidence or mortality of neuroblastoma, osteosarcoma, Ewing sarcoma, or retinoblastoma, instead placing them into an "other cancer" group. Taken together, extra-cranial solid tumors represent 17% of childhood cancers in HIC and they probably account for a large proportion of the uncategorized childhood cancers in Table 1. This is particularly relevant due to the growing body of genetic predisposition data and observed variations in the global incidence of solid tumors among children.(20, 38) Additionally, although in the GBD study years-lived with disability (YLDs) and DALYs are estimated, up to now, these estimates have not taken into account the specific long-term treatment associated chronic health conditions that occur in childhood cancer survivors.(39-41) Finally, although GBD categorizes all pediatric data, inclusive of the adolescent group, into 5-year age groups, 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. A recently published manuscript focusing on the global burden of cancer among AYA patients utilized GLOBOCAN methods and has reported global incidence and mortality outcomes for the 20- to 39-year age group.(42)

Beyond differences in data preparation and modeling methods, a key gap with no obvious solution that remains a critical void 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 may both result in

underestimation of the true cancer burden. This is particularly important when interpreting GLOBOCAN estimates as they are a reflection of the true diagnosed cancers. GBD attempts to quantify the total underlying burden – diagnosed *and* undiagnosed by adjusting for so-called "garbage codes" (causes of death that should not be coded as the underlying cause of death or undefined codes like ICD-10 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 through increasing diagnostic capacity and access to care, as well as through the validation of additional covariates when modeling pediatric cancer incidence.

An appreciation of all these limitations is critical 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. 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 an underdiagnoses, through likely misidentified or never identified new cases or deaths, the interpretation changes. Thus, investigators should not assume that the available estimates reflect the true incidence of childhood cancer in LMIC. Rather, these data should be interpreted as the number of cases of childhood cancer being identified and seeking treatment within the health system, a still important finding with practical health-services planning implications.

Recommendations by the authors to improve estimation methods for the global cancer burden in children and adolescents

The objectives and methodology 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 emphasize the global burden of childhood cancer in the absence of adapted sources.(2, 43, 44) However, there is a need to critically compare or appraise the methods currently used and propose improvements in the current estimation approaches used.

Panel 1 presents a list of proposed steps and initiatives as recommended by the authors to improve pediatric 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 pediatric cancer registries that can represent the basis of evidence-based childhood cancer control plans. Given the paucity of quality-assured incidence data in LMIC, technical assistance to 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 in order to improve the quality of reported registry data (i.e., reporting delay adjustments).(45) There is an overwhelming need for a multi-stakeholder action plan that emphasizes the use of observed data through increasing childhood cancer registry capacity in LMIC to inform dedicated childhood cancer control plans. The Global Initiative for Cancer Registration Development,(46) led by IARC with multiple global partners, represents an example of such an initiative.

Incorporating childhood cancer into the global prioritization framework and developing more high-quality population-based cancer registries is a critical long-term investment, although the short-term step in improving current estimates should involve use of adapted cancer categories such as the ICCC whenever ICD-O-3 data is available.(17) Due to small numbers, many childhood cancers are currently grouped into broad categories that are not clinically meaningful. For example, leukemias, lymphomas, central nervous system tumors and other heterogeneous tumor subgroups should be defined by a common standard (currently ICCC-3) and categorized into subgroups that are relevant from a public health and clinical perspective. The most obvious example where this is relevant is when overview studies collapse ALL and AML into a single "leukemia" category. Although these two diagnoses are often grouped together, based on historic convention and small numbers due to the low ALL compared to AML incidence in the adult population, they are different cancers with a substantial burden among children, and hence, should be reported separately for health planning purposes. However, simply applying all 48 ICCC-3 categories in order to eliminate the proportion of uncategorized 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. Thus, careful appraisal of how categories are currently grouped, particularly for the unspecified and other specified neoplasms, is an important exercise that should be conducted and justified by each overview study.

Reexamination of the adapted cancer categorization systems themselves such as ICCC-3 is also needed. For example, lymphoblastic lymphomas, currently classified with other non-Hodgkin lymphomas based on historic convention, would be better categorized with ALL, given the similar biology and treatment. Similarly, segregating embryonal tumors, low-grade gliomas and high-grade gliomas as distinct central nervous system 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 make these classification categories feasible.

Moreover, without access to multidisciplinary treatments, including cytotoxic chemotherapies, radiation, surgery and high-quality supportive care, childhood cancer is a fatal disease. Thus, incidence data, while critical for health services planning, need to be paired with access and outcomes data when contextualizing 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, while estimates of the cancer burden derived from models cannot replace the real observed data, they can help galvanize interest and to 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 on staging of childhood cancers,(47) 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.(48)

Childhood cancer burden estimates: Policy implications

With the advent of the Sustainable Development Goals(49) and the global drive towards universal health coverage by 2030, the World Health Assembly recently 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 2013-2020.(50) 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 current global childhood cancer burden estimates is an important prerequisite. For countries where population-based cancer registries exist, the observed data from these sources may 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, highlighted in figure 4, should serve as an incentive to establish suitable surveillance systems in each country.

Although several publications have recently demonstrated that childhood cancer treatment is cost-effective,(51) affordability and financial toxicity are also known barriers to successful pediatric cancer control initiatives that require policy interventions.(52, 53) The private sector has provided a significant amount of funding to support childhood cancer treatment programs in LMIC.(54, 55) If organizations 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 expand fundraising efforts by demonstrating 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 that reported the survival and costs associated with treating children with ALL, the Chinese Ministry of Health decided in 2010 to provide governmental funding to treat all children with the disease.(56)

Conclusions

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 pediatric 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 include expanding the coverage of childhood cancer registration, especially in LMIC; enhancing the quality of data collection through capacity-building and standardized data dictionaries; and development of training curricula for tumor 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. Thus, the results from these sources are highly heterogeneous. Due to the substantial differences between the estimates, making confident decisions on health policy, priority setting, and cancer control strategy and financing based on the available information is currently a challenging prospect.

Table 1: Comparison of Currently Available Data on Global Pediatric Cancer Burden Approaches

	IICC-3(12)	GLOBOCAN 2012(13)	GBD 2016(26)	CONCORD-3(15)
Publication year	2017	2015	2017	2018
Years included in study	2001-2010	2012	1990-2015	2000-2014
Coordinating Organization	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 and low-middle income countries*	11%	7%	12%	5%
Countries/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***	Leukemias****,****** Lymphomas, CNS tumors, Neuroblastoma, Retinoblastoma, Kidney, Hepatic, Bone, Soft Tissue, Germ cell, Epithelial tumors, Other and unspecified	Leukemias****, Hodgkin, NHL, CNS, Kidney*****, Liver*****, Kaposi Sarcoma	ALL, AML, Hodgkin, NHL, CNS, Kidney*****, Liver*****	Acute lymphoblastic leukemia******, Lymphomas, CNS tumors
Uncategorized 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

IACR: International Association of Cancer Registries, 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;

* Low income and low middle-income country percentages calculated based on World Bank Fiscal Year 2018. Upper-middle income countries not included in the proportions reported.

**Cancer coding may differ between the original data and the categories according to which they are presented.

***ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; CNS: Central nervous system tumors; NHL: Non-Hodgkin lymphomas. ****ALL and AML not estimated separately;

*****Kidney/Liver: Topographic codes in GLOBOCAN and GBD, Histology included in IICC-3.

******Leukemias were further stratified into ALL and AML in a CONCORD-2 sub-analysis and in the open-access online data from IICC-3.

Table 2: Differences between the methods for modeling incidence and mortality in GLOBOCAN 2012 and GBD 2016

Study	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 (sub-)national population-based cancer registries and vital statistics of the index country or region	Based on modeled mortality estimates using separately modeled mortality-to-incidence ratios
Mortality estimation	Estimation from local, regional, pooled and neighbor 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 modeled 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 LMIC	Data presented according to ICD site codes, which do not reflect with the major childhood cancer diagnostic groups. Information from pediatric cancer registries was not considered.	Data presented according to ICD site codes, which do not reflect with the major childhood cancer diagnostic groups. Information from pediatric cancer registries was not considered. Adult mortality-to-incidence ratios were used to estimate childhood cancer incidence from childhood mortality data.

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

Malignancy ranked based on SEER incidence ages 0-14 years**	Number of cases			Number of deaths		
	GLOBOCAN 2012	Global Burden of Disease (GBD) 2016 (UI)	Ratio******	GLOBOCAN 2012	Global Burden of Disease (GBD) 2016 (UI)	Ratio******
Leukemias***	49,752	63,230 (57,517-67,989)	1·27	27,775	29,165 (26,846-32,673)	1·05
Acute lymphoblastic leukemia	not estimated	30089 (28,217-33,082)	-	not estimated	12,489 (11,429-14,828)	-
Acute myeloid leukemia	not estimated	11,631 (10,376-13,178)	-	not estimated	5,811 (5,030-6,840)	-
Brain, nervous system tumors	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	7,223	10,974 (9,195-12,375)	1·52
Kidney tumors (mostly Wilms' tumor)****	9,656	13,794 (12,988-14,437)	1·43	5,547	2,481 (2,305-2,654)	0·45
Bone tumors	not estimated	not estimated	-	not estimated	not estimated	-
Hodgkin lymphoma	6,744	5,220 (4,270-5,946)	0·77	1,737	2,421 (1,798-3,069)	1·39
Rhabdomyosarcoma	not estimated	not estimated	-	not estimated	not estimated	-
Retinoblastoma	not estimated	not estimated	-	not estimated	not estimated	-
Categorized 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
Uncategorized cancers*****	49,082	51,184 (46,850-54,878)	1·04	22,095	20,048 (18,287-22,478)	0·91
Proportion uncategorized	0·3	0·28	-	0·28	0·24	-

GBD 2016 provided estimates of incidence and mortality for 195 countries, GLOBOCAN 2012 for 184 countries, so only countries included in both studies were included in the totals and the ratios. All estimates reflect 2012 figures.
*UI: Study generated 95% uncertainty interval.
** 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.
***GLOBOCAN 2012 does not differentiate Leukemia based on WHO type. GBD 2016 estimates "other leukemias" in addition to ALL and AML.
****Neither group estimates Wilms tumor as a separate entity, however, as Wilms tumors represent a substantial majority of childhood kidney cancers where reliable histopathology incidence data are available, kidney tumors in this age group were assumed to represent primarily Wilms' tumors.
*****Uncategorized: cases included under "other neoplasms" category.
******Ratio based on the absolute global number of row-specific childhood cancers reported in GBD to GLOBOCAN.
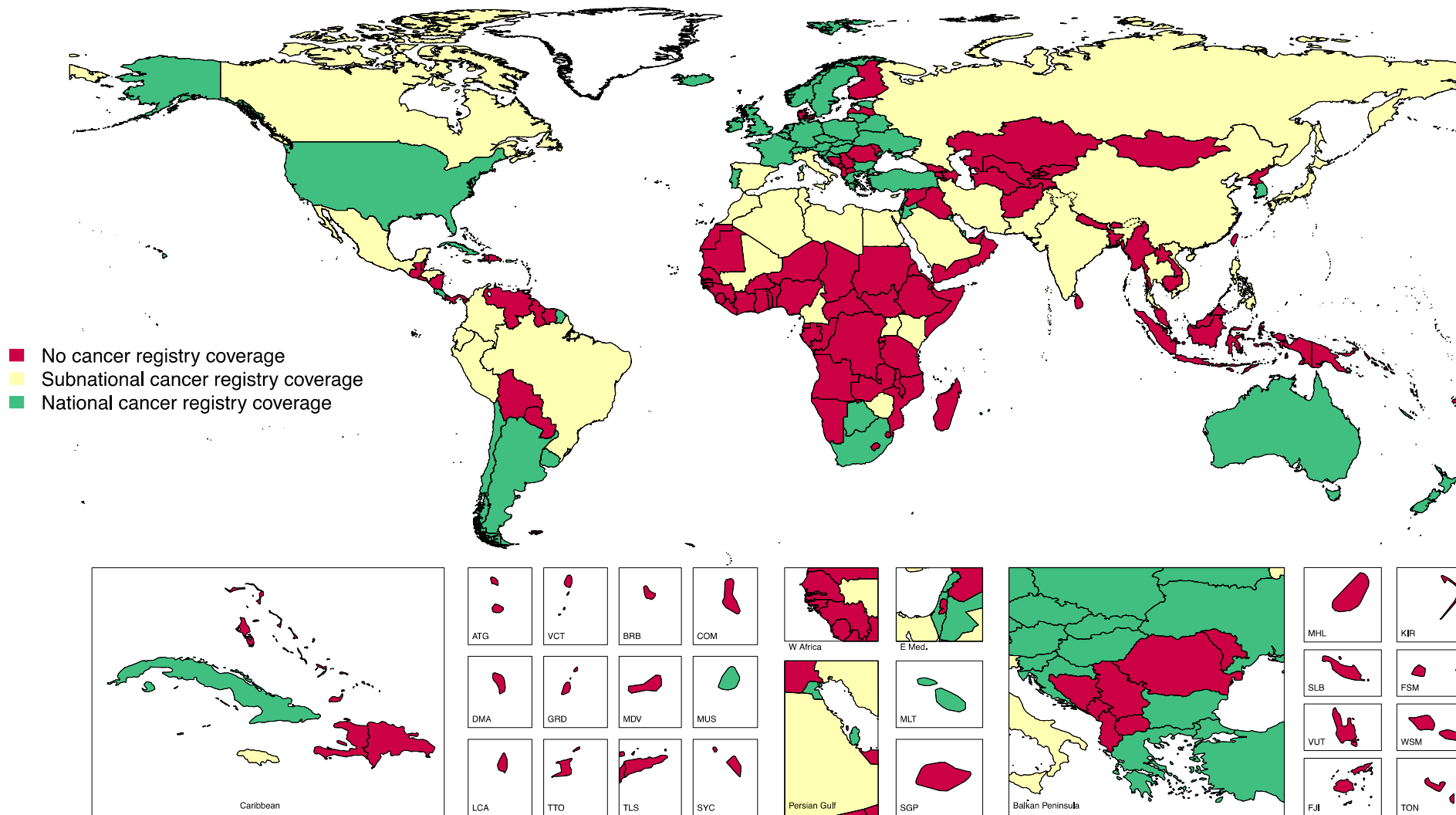
Figure 1: Global Pediatric Cancer Registry Coverage Based on Registries Contributing to the Final IICC-3 Study(11)*
The figure reflects the 308 high quality population-based cancer registries included in the study the IICC-3.

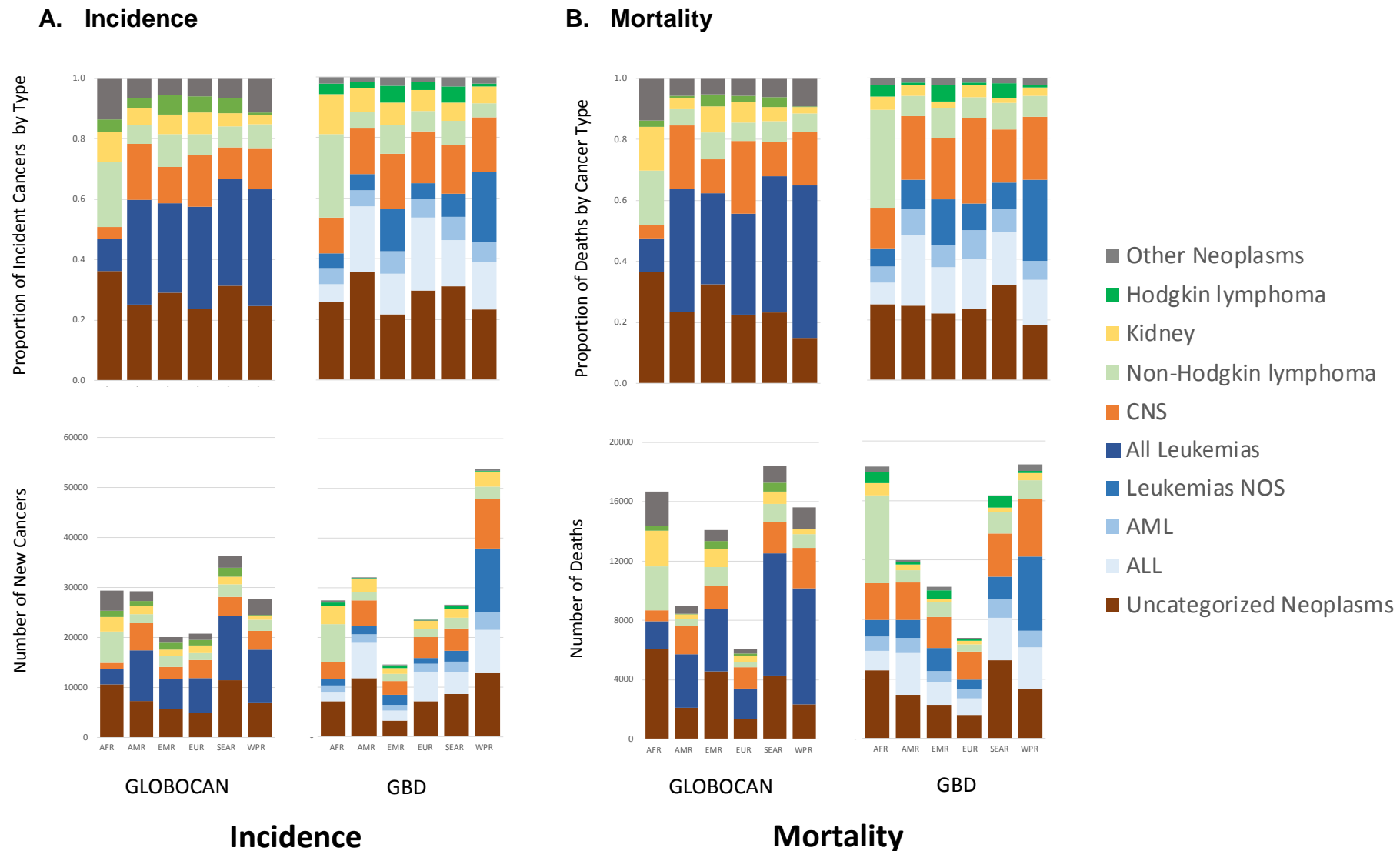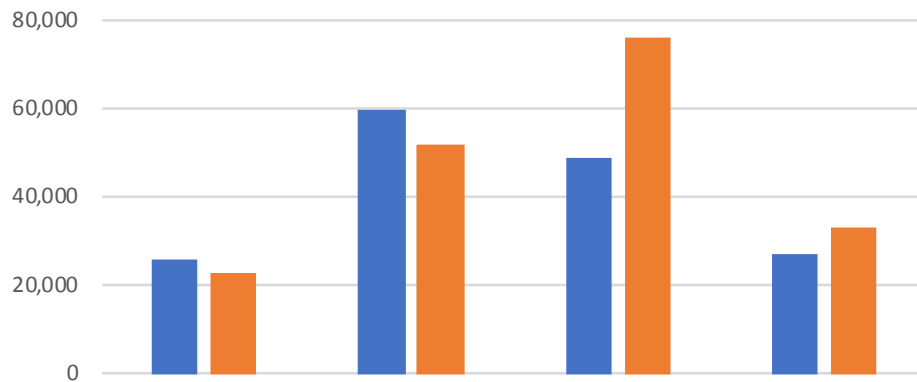**A. Incidence**

B. Mortality

Figure 2: Proportion and Absolute Number of Cancer Cases in Children (Age 0-14 years) (A) Incidence and (B) Mortality by Type and World Health Organization (WHO) Region*

*Regional designations as defined by the WHO: AFR=African, AMR=Americas, EMR=Eastern Mediterranean, EUR= European, SEAR=Southeast Asia, WPR=Western Pacific; Leukemia NOS=Leukemia not otherwise specified. *Reference year 2012 data for GBD 2016 were used to compare estimates between studies.*
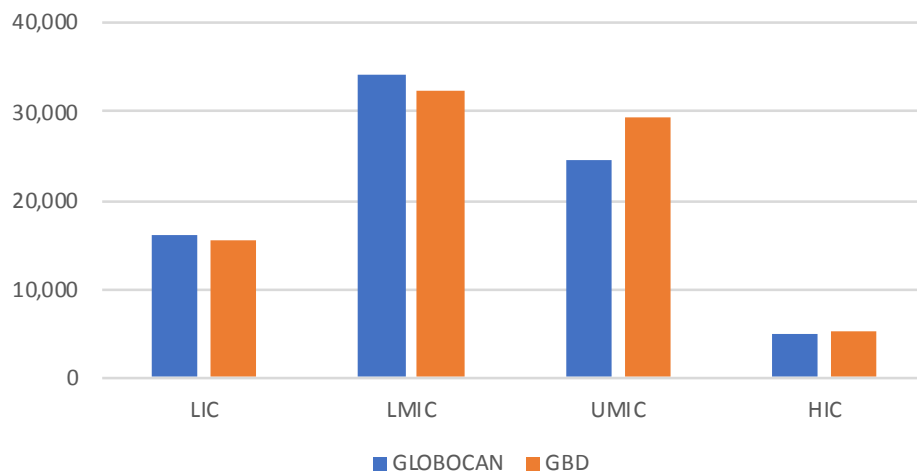
A. Incidence

B. Mortality

Figure 3: Absolute Number of Overall Cancer (A) Incidence and (B) Mortality Cases in Children (ages 0-14 years) by 2012 World Bank Low- and Middle-Income Status*
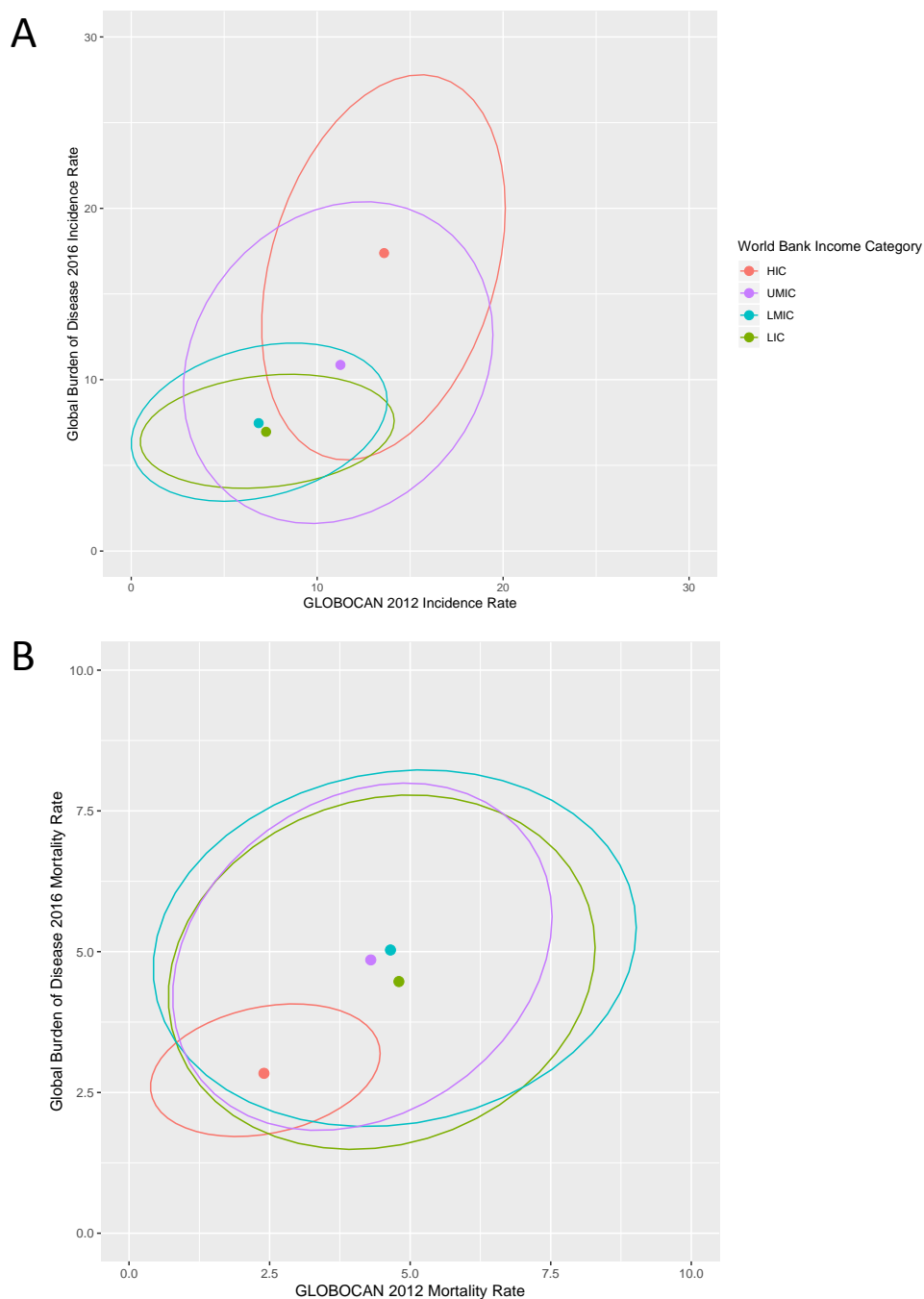*Reference year 2012 data for GBD 2016 were used to compare estimates between studies.*

Figure 4: Overall Childhood (A) Incidence and (B) Mortality Rates in Children (ages 0-14 years)*

Dark shaded dots correspond to the median GLOBOCAN 2012 (x-axis) and GBD 2016 (y-axis) rates for incidence (Panel A) and mortality (Panel B) by countries categorized using the World Bank Income Groupings. Lighter shaded dots correspond to country-specific incidence (Panel A) and mortality (Panel B) rates, age-standardized per 100,000 children 0-14 years. 95% confidence ellipses correspond to the income group by color. 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 final figures and median calculations due to reported outlier rates but data is included in the appendix. *Reference year 2012 data for GBD 2016 were used to compare estimates between studies.

Panel 1: Recommendations from authors to improve estimates of the childhood cancer burden

- Support existing cancer registries to improve the quality of childhood and adolescent ICD-O-3 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 cancer patients, 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.

- Use cancer categories which are relevant for childhood cancers and clinically meaningful for both observed and modeled data, and report outcomes using the ICCC-3 groupings. Results should be reported separately for the subgroups of leukemia and lymphoma and CNS tumors should be reported by grading. Reports should include results for major solid tumors common in childhood age.

- Develop models, using appropriate classification approaches, to forecast the expected changes in cancer incidence among children based on demographics shifts, potential reductions in non-communicable disease and diagnostic capabilities.

- Develop statistical approaches to integrate data from large cancer survivorship studies in order to include cancer treatment related chronic health conditions when estimating DALYs.

- 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, 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 sub-classes for analysis and reporting.

- Create and disseminate cancer registration training curricula and opportunities that are specific for childhood cancer.

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