Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: http://ees.elsevier.com

Childhood cancer: A global perspective

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Accounting for less than 1 % of all malignancies diagnosed worldwide, cancer in children under 15 years of age is rare, and the spectrum of neoplasms that occur tend to differ in important respects from those seen at older ages; not only with respect to their biological characteristics and behaviour, but also with respect to their symptom profiles, modes of presentation, treatment options and outcomes. Often presenting with general symptoms that can be confused with other conditions and illnesses, the majority of childhood cancers cannot be diagnosed without access to sophisticated technologies, and cannot be treated without access to effective cancer therapies and supportive care; in all situations clinical specialists are required in order to recognize and make the diagnosis (e.g. pathologists and radiologists), and manage the condition (e.g. paediatric oncologists and haematologists) [1–3].

Unsurprisingly then, when it comes to cancer outcomes, the global disparities seen for childhood cancer could hardly be wider. In high-income countries, where less than 10 % of the world's childhood population live, five-year net survival (all childhood cancers combined) currently exceeds 80 %, and is continuing to improve as new technologies and treatments emerge [4]. Indeed, in these settings the focus is changing rapidly, with clinical trials targeting treatment optimisation (especially treatment intensity to reduce treatment-related toxicity), and research focussing on the reduction of somatic and late effects [5]. By contrast, in the rest of the world most children with cancer die from their disease, having never been diagnosed or treated [1,2,6]. In Kenya, for example research has shown that many parents: i) cannot afford costs related to treatment, or even the costs of repeated visits to hospital, often deciding not to return after hearing the suspected diagnosis; ii) seek traditional treatment and delay going to hospital because they fear hospital detention if they can't pay, and so when they finally attend hospital, the disease is at an advanced stage; iii) sometimes have to abandon their detained child at the hospital if they are not able to pay hospital bills [7].

With around three-quarters of the world's population living in countries that are not covered by cancer surveillance systems, quantifying the underlying global burden of any cancer is challenging [1,8,9]. Over and above this, producing accurate estimates on the occurrence and survival for many childhood tumours is further complicated by the particularly high levels of underdiagnosis in low-income countries, and to some extent, middle-income countries. In many of these settings, childhood morbidity and mortality from infectious and parasitic diseases dominate, and the likelihood of missing childhood cancers presenting with symptoms of infection such as fever (e.g. acute lymphoblastic leukaemia - the commonest childhood cancer) or vomiting and weight loss (e.g. brain tumours) is compounded by their rarity and lack of knowledge about the cancers themselves. Such underdiagnosis, explains why tumours with external characteristics (e.g. retinoblastoma) that make them relatively easy to recognize (albeit at a late stage) are relatively high in some less economically developed regions of the world [9,10]; and why, for example, a detailed analyses of South African childhood cancer incidence data demonstrated less under-ascertainment for cancer types with clearly visible symptoms than it did for those with nonspecific symptoms (e.g. haematological cancers and brain tumours) [11].

This Special Issue presents a snapshot of the present situation in relation to childhood cancer in different parts of the world, examining methods for estimating the global burden and geographic variations [9], and comparing patterns of care in high-income countries [12] with different exemplar regions of middle-to-low income countries in Latin American [13], the Middle East and North Africa [14], and India [15]. Undoubtedly, the information presented confirm the need for sustainable care for children in less well-resourced settings [2]. However, it needs to be understood that the challenges to diagnosis and access to treatment not only impact on survival and survivorship, but also impact on measuring the burden of childhood cancer and the identification of their causes. Cancer registries can only measure cancers identified in the healthcare system, naturally missing undetected cases and those without a verified diagnosis; evidently in many parts of the world this comprises the majority of cases. So rather than measuring incidence, they can only measure the occurrence of diagnosed disease. The global burden of diagnosed childhood cancer cases is estimated to be about 151,435 cases per year [10]. Attempts to correct for under-ascertainment and estimate incidence, using the baseline model described in this Special Issue [9] and other ways of extrapolation [6] produce estimates of 360,114 and 396,670 per year respectively. More than double the estimate from cancer registration alone, these estimates are likely to be much closer to the true underlying incidence; supporting the call for increased development of

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https://doi.org/10.1016/j.canep.2020.101878
Received 7 December 2020
Available online xxx
1877-7821/

childhood cancer registration and upscaling of surveillance [16]. It is also important to note that referral bias does not only vary by geography, between and within countries, but also by other variables, such as socioeconomic status and other demographic indicators. A notable observation comes from India, where the male-to-female incidence rate ratio for all childhood cancers combined is 1.56, which is significantly higher than the 1.15 observed elsewhere in the world [15]. Whereas the latter is a consequence of biology, the bias in India reflects the general Southeast Asian preference for male children. Such gender-biases impact on behaviours in many areas of life; the sex differential for childhood cancer being due to healthcare not be sought for female children who fall ill.

High quality descriptive disease patterns and trends form the foundation of health care planning and aetiological hypotheses for further investigation. The findings presented in this Special Issue highlight the need for a cautious interpretation of the observed geographic differences in childhood cancer, which have previously provided the foundation of several aetiological hypotheses; notably the suggestion that exposures linked to poverty may protect against certain cancers, including acute lymphoblastic leukaemias and tumours of the central nervous system that occur in children. Notably, however, aside from exposure to relatively high doses of ionizing, previous chemotherapy and infection (Burkitt lymphoma and Kaposi sarcoma), few targets for prevention of these cancers have, in fact, been established so far [3,17]. Furthermore, developed countries with presumably complete childhood cancer registration systems and accurate population denominators tend to have very similar incidence rates, regardless of differences in environmental conditions – suggesting that environmental exposures may not play the same aetiological role in childhood cancers as they do in adult cancers [18]. For example, the incidence rates of lymphoid leukaemia in children are practically identical at about 43 per million per year in the geographically diverse regions of Australia, Germany and Canada [10], where marked variations have been demonstrated for several adult cancers with known environmental causes [19] (e.g. smoking-, diet-, alcohol-, occupation- and infections-related cancers, all investigated with regard to parental exposures and risk of lymphoid leukaemia in their offspring (17)). Hence, for most childhood cancers the evidence suggests that future aetiological hypotheses should be compatible with geographical similarities, rather than with geographical differences which are heavily affected by underdiagnosis - exceptions being those childhood cancers with well-established associations with infection that are largely confined to low-income countries.

A positive development in recent years, is that the increasing awareness of the unacceptable nature of the childhood cancer situation, which is resulting in major initiatives for improvement being started. The World Health Organisation (WHO) for instance launched the Global Initiative for Childhood Cancer, which "*aims to increase survival of children with cancers worldwide to* > 60 % *by 2030 by promoting access to high-quality cancer care for all children and with an initial focus on common and curable cancer types.*" [20]. Local schemes also already exist; and in this Special Issue, researchers from Uganda describe how, with limited resources, they have approached improving outcomes for retinoblastoma [21], one of the few childhood malignancies that presents with recognizable external signs and may in fact, like Burkitt lymphoma, have a higher incidence in certain less well developed regions of the world [9,22]. While a long rocky road may still lie ahead, some improvements are mainly a matter of resources, while others may need more time for implementation.

Author contribution

This editorial was written jointly by JS and ER.

Funding

The planning and organisation of this Special Issue received support from the German Federal Office of Radiation Protection (BfS) [grant number: 3614S30041] to the Global Acute Leukemia network (GALnet, http://galnet.iarc.fr (accessed November 1, 2020)).

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Declaration of Competing Interest

The authors report no declarations of interest.

References

[1] I. Magrath, E. Steliarova-Foucher, S. Epelman, R.C. Ribeiro, M. Harif, C.-K. Li, et al., Paediatric cancer in low-income and middle-income countries, Lancet Oncol. 14 (March 3) (2013) e104-16.
[2] R. Atun, N. Bhakta, A. Denburg, A. Frazier, P. Friedrich, S. Gupta, et al., Sustainable care for children with cancer: a Lancet Oncology Commission [Internet]. Vol. 21, The Lancet. Oncology, Lancet Oncol (2020) [cited 2020 Dec 2]. Available from: https://pubmed.ncbi.nlm.nih.gov/32240612/.
[3] E. Roman, T.J. Lightfoot, S.V. Picton, S.E. Kinsey, Childhood cancers, in: M.J. Thun, M.S. Linet, J.R. Cerhan, C. Haiman, D. Schottenfeld (Eds.), Schottenfeld and Fraumeni Cancer Epidemiology and Prevention, 4th ed., 2017 (Schottenfeld and Fraumeni Cancer Epidemiology and Prevention, Fourth Edition).
[4] R.C. Ribeiro, E. Steliarova-Foucher, I. Magrath, J. Lemerle, T. Eden, C. Forget, et al., Baseline status of paediatric oncology in ten low-income or mid-income countries receiving my child matters support: a descriptive study, Lancet Oncol. 9 (August 8) (2008) 721.
[5] F. Erdmann, L.E. Frederiksen, A. Bonaventure, L. Mader, H. Hasle, L.L. Robison, et al., Childhood cancer: survival, treatment modalities, late effects and improvements over time, Cancer Epidemiol. (May 24) (2020) 101733.
[6] N. Bhakta, L.M. Force, C. Allemani, R. Atun, F. Bray, M.P. Coleman, et al., Childhood cancer burden: a review of global estimates, Lancet Oncol. 20 (January 1) (2019) e42-53.
[7] S. Mostert, F. Njuguna, Burgt R.H.M van der, J. Musimbi, S. Langat, J. Skiles, et al., Health-care providers' perspectives on health-insurance access, waiving procedures, and hospital detention practices in Kenya, Pediatr. Blood Cancer 65 (8) (2018) e27221.
[8] J. Ferlay, M. Colombet, I. Soerjomataram, C. Mathers, D.M. Parkin, M. Piñeros, et al., Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods, Int. J. Cancer 144 (8) (2019) 1941–1953.
[9] W.T. Johnston, F. Erdmann, R. Newton, E. Steliarova-Foucher, J. Schüz, E. Roman, Childhood cancer: estimating regional and global incidence, Cancer Epidemiol. (January 7) (2020) 101662.
[10] E. Steliarova-Foucher, M. Colombet, L.A.G. Ries, F. Moreno, A. Dolya, F. Bray, et al., International incidence of childhood cancer, 2001–10: a population-based registry study, Lancet Oncol. 18 (January 6) (2017) 719–731.
[11] F. Erdmann, D. Kielkowski, S.J. Schonfeld, P. Kellett, M. Stanulla, C. Dickens, et al., Childhood cancer incidence patterns by race, sex and age for 2000–2006: a report from the South African National Cancer registry, Int. J. Cancer 136 (June 11) (2015) 2628–2639.
[12] Kinsey S., Picton S.V., Childhood Cancer in High Resource Settings. Cancer Epidemiol. (in print)
[13] C.P.C. Guzman, M.A. Cordoba, N. Godoy, A. Castaño, K.B. Ribeiro, F. Moreno, et al., Childhood cancer in Latin America: from detection to palliative care and survivorship, Cancer Epidemiol. (October 26) (2020) 101837.
[14] M. Basbous, M. Al-Jadiry, A. Belgaumi, I. Sultan, A. Al-Haddad, S. Jeha, et al., Childhood cancer care in the Middle East, North Africa, and West/Central Asia: a snapshot across five countries from the POEM network, Cancer Epidemiol. (June 2) (2020) 101727.
[15] S. Ganguly, S. Kinsey, S. Bakhshi, Childhood cancer in India, Cancer Epidemiol. (February 6) (2020) 101679.
[16] M. Piñeros, L. Mery, I. Soerjomataram, F. Bray, E. Steliarova-Foucher, Scaling up the surveillance of childhood cancer: a global roadmap, J. Natl. Cancer Inst. (May 20) (2020).
[17] J. Schüz, F. Erdmann, Environmental exposure and risk of childhood leukemia: an overview, Arch. Med. Res. 47 (November 8) (2016) 607–614.
[18] J. Schüz, C. Espina, C.P. Wild, Primary prevention: a need for concerted action, Mol. Oncol. 13 (March 3) (2019) 567–578, doi:10.1002/1878-0261.
[19] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (November 6) (2018) 394–424, doi:10.3322/caac.21492.
[20] I. Chitsike, V. Paintsil, L. Sung, F. Njuguna, A. Mavinkurve-Groothuis, F. Kouya, et al., Working together to build a better future for children with cancer in Africa, JCO Glob Oncol. 6 (July) (2020) 1076–1078.
[21] K. Waddell, M. Matua, C. Bidwell, R. Atwine, J. Onyango, S.V. Picton, et al., A ten-year study of Retinoblastoma in Uganda: an approach to improving outcome with limited resources, Cancer Epidemiol. (July 10) (2020) 101777.
[22] Global Retinoblastoma Study Group, I.D. Fabian, E. Abdallah, S.U. Abdullahi, R.A. Abdulqader, S. Adamou Boubacar, et al., Global retinoblastoma presentation and analysis by national income level, JAMA Oncol. 6 (May 5) (2020) 685–695.