Title: Psychosocial consequences of surviving cancer diagnosed and treated in childhood versus in adolescence/young adulthood: A call for clearer delineation between groups

Anne-Sophie E Darlington1, Claire E Wakefield 2,3, Loes ME van Erp4, Winette TA van der Graaf5,6, Richard J Cohn2,3, Martha A Grootenhuis4.

1School of Health Sciences, University of Southampton, Southampton, United Kingdom

2Kids Cancer Centre, Sydney Children's Hospital, Sydney, NSW, Australia

3Behavioural Sciences Unit, School of Clinical Medicine, Faculty of Medicine and Health, UNSW Sydney, NSW, Australia

4Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

5Netherlands Cancer Institute, Department of Medical Oncology, Amsterdam, The Netherlands

6Erasmus Medical Centre Cancer Institute, Department of Medical Oncology, Erasmus University Medical Center, Rotterdam, The Netherlands

**Corresponding author:**

Professor Anne-Sophie Darlington

School of Health Sciences

University of Southampton

Highfield Campus

University Road

Building 67

SO171BJ Southampton

United Kingdom

Tel. +44 2380597888

Email: a.darlington@soton.ac.uk

**Running title**: Surviving cancer in childhood versus in adolescence/young adulthood

**Funding**: None

**Conflicts of Interest**: None

The number of young people who have survived cancer continues to grow worldwide.1 Alongside this welcome medical achievement, there is now increasing recognition of the importance of evaluating and supporting the psychosocial needs of these young cancer survivors.2 Significant progress has been made in improving understanding of the needs of young cancer survivors and in developing interventions to meet these needs.3 One aspect that warrants more attention and discussion is the impact of the young person’s stage of development at the time of their diagnosis and treatment on longer term psychosocial outcomes.

Currently, in the literature, the distinction between young survivors of cancers diagnosed in childhood, adolescence, and young adulthood is often not clear. Often, the needs of young people who have survived childhood cancer are merged with the needs of young people who have survived adolescent or young adult cancer.4-6 Lack of clarity around the defined age range for adolescents and young adults in the field adds additional challenges. In other instances, there is a lack of clarity as to which group of young survivors is being described.7, 8

In this commentary, we hypothesise that developmental stage at cancer diagnosis, and the interruptions experienced in achieving developmental milestones, is central to the experience of having and surviving cancer, and can influence subsequent outcomes as a survivor. We posit the need for assessment of the potential psychosocial differences between survivors of cancer diagnosed during childhood [‘Childhood Cancer Survivors’ or ‘CCS’] and survivors of cancer diagnosed during adolescence and young adulthood [‘Adolescent and Young Adult Cancer Survivors’ or ‘AYACS)’]. There is wide variability in the age ranges used to delineate children from adolescents and young adults in the literature,9 however the focus of this commentary will be on the experiences of childhood cancer survivors who were diagnosed before the age of 16 (CCS), and comparing their experiences with those diagnosed during adolescence and young adulthood, i.e. from age 16 to 25 years (AYACS).

We define survivors as those who are at least five years since their cancer diagnosis. In this commentary, we draw attention to the challenges in appropriately meeting the psychosocial needs of these two groups when definitions and terminology used are unclear. We conclude by calling for each group to receive separate research and clinical attention.

**CCS and AYACS experience different developmental interruptions**

It is unlikely that the experience of receiving a cancer diagnosis and undergoing cancer treatment in children and adolescents/young adults can be the same in light of rapid developmental changes young people experience during these years. It is crucial to place the experience of having cancer in the context of this development.

Infancy is dominated by emotional development, dependence, trust and parental relationships. The pre-school period is influenced by cognitive development and characterized by egocentric and magical thinking, and associative logic, as well as development of self-regulation. The school-age period is then dominated by the development of logical thinking, increased awareness of self, and the increasing importance of social interactions. These stages correspond to Child Development stages as set out by Erikson10,11 with stages focused on Autonomy, Initiative and Industry from 2-12 years of age, the Identity stage from age 13-18 years of age, and Intimacy being important from age 18 years. Receiving a cancer diagnosis during early childhood therefore potentially disrupts early social skills development, early childhood education (e.g. pre-school and early school years),3 and family functioning.12 CCS, in particular those diagnosed at very young age, may not always remember their lives ‘before cancer’ and potentially have limited understanding of their illness and treatment.13 Their parents may not have shared all details regarding their cancer experience with them and likely took responsibility for making medical decisions on behalf of their child.13 This may mean that CCS are heavily dependent on their family’s narrative of their cancer experience, and their parents’ medical knowledge gained throughout treatment.

This issue, being dependent on the family’s narrative of the cancer experience, has clinical implications. For some CCS who were diagnosed when they were very young, especially those who may be lost to follow-up early, knowledge of their treatment and risk of late effects may be very limited and affect their adherence to surveillance guidelines. This has implications for education and the design of models of care for survivorship/long-term follow-up. This concept is relevant also in relation to meeting the needs of the two populations, discussed below. A key challenge for CCS then can be to “catch up” on key early developmental milestones, especially during the transition from adolescence to young adulthood. CCS need to adjust earlier in life than AYACS to living with the consequences of the treatment of their cancer.

Adolescence features the development of abstract thinking, identity formation and the search for independence, which begin to be realized in early adulthood.14 Having cancer as an adolescent or young adult therefore disrupts critical, but different, developmental milestones to having cancer as a child. AYACS have a lived (and remembered) experience of their life before their cancer, as well as potentially more awareness or understanding of the implications of their cancer diagnosis and treatment. They may be less likely than CCS to rely on their parents to “fill in the gaps”. However, a diagnosis during adolescence and young adulthood may significantly disrupt autonomy and identity development for young people.10,11,15 In some instances, young adults who have recently moved out of their family home return, due to their medical treatment and support needs, impacting their development and family and social relations. Concrete milestones for AYACS after their cancer experience then include progressing or completing formal education, pursuing and keeping employment, moving out of home, earning an income, developing romantic and sexual relationships, and having children.

It is important to acknowledge that even within the CCS group, there is a range of survivors diagnosed and treated in early childhood, through to those treated in early adolescence. Their experiences will be related to the stages of the child's cognitive development at cancer development (according to Piaget16). Some distinctions can be made between pre-operational thinking (approximately <7 years), concrete operational thinking (approximately 6-12 years) and formal operational thinking (approximately >12 years). Memories and experiences will be colored by these phases. The adolescent who thinks formally operationally can imagine and apply abstraction, is able to reason, can think beyond the present, and can consider complications and long-term consequences of illness and treatment.

All stages have their particular milestones and achievements. The achievements of social, academic, and professional competence, peer relationships, independence from parents and identity are generally recognized as important milestones in the development of a child into young adulthood. Diagnosis of cancer before particular transition points in life, which are essential in terms of development in social functioning, could delay or disrupt this development.

**CCS and AYACS may experience different psychosocial challenges, but the data is unclear**

Evidence suggests that subgroups of both CCS and AYACS experience psychosocial challenges in survivorship.3 Data are however lacking that clearly distinguish the outcomes and needs of these two groups, despite experiencing different developmental interruptions. We posit that CCS and AYACS are likely to have:

1) Some similar psychosocial outcomes caused by similar experiences. For example, a subset of CCS and AYACS experience mental health challenges after completion of their cancer treatment, possibly due to a similar need to process their cancer experience, feeling ‘different’ from their peers, experiencing changes in their relationships, and worrying about cancer recurrence;12

2) Some similar psychosocial outcomes, with different experiences driving these outcomes. For example, while CCS and AYACS can both experience concerns regarding sexual functioning and fertility, it is less likely that CCS were sexually active or had made concrete family planning decisions before their cancer diagnosis. AYACS in contrast, may need to adjust to new sexual functioning post-cancer and contemplate the impact of cancer on their previous expectations about starting a family; and

3) Some different psychosocial outcomes because they experienced different developmental interruptions. For example, while data directly comparing cognitive outcomes for CCS versus AYACS are sparse, cognitive difficulties may be more pronounced for CCS, for whom the achievement of early, yet foundational, cognitive milestones (e.g. literacy and numeracy) may have been significantly disrupted. In contrast, AYACS may have had their attendance and engagement during the final years of high school/university disrupted, compromizing development of higher order cognitive skills.17-19

**A call for clearer delineation when assessing the needs of CCS and AYACS**

While it is clear that CCS and AYACS experience differing developmental trajectories, the lack of clear delineation between these two groups in the literature makes it difficult to understand, and therefore meet, the psychosocial needs of these two growing populations. As summarized by Figure 1, the lack of delineation between groups in current research has the potential to reduce researchers’ and clinicians’ ability to understand the specific needs of each group of young people. There is a need for a clear theoretical underpinning of research in this area, based on our understanding of child, adolescent and young adult development.

Blurring CCS with AYACS impairs our ability to differentiate their age-specific needs and develop evidence-based interventions for each group. Without accurate understanding of CCS’ and AYACS’ needs, it is difficult to provide tailored psychosocial care for young cancer survivors. It is also difficult to raise awareness and advocate for the needs of young people who have survived cancer. It is time to move beyond generic studies which merge CCS and AYACS together, and beyond studies that do not clearly define their cohorts. By identifying the similarities and differences between CCS and AYACS more clearly, future research and care will be able to provide more targeted and appropriate supports for all young people after surviving cancer.

We acknowledge the influence of treatment and diagnosis (particularly for brain tumours) on developmental, physical and cognitive outcomes. The proposed framework proposes to create awareness in order for future research to tease out the influence of development and age at diagnosis on long-term outcomes, with attention for likely differences and similarities. The influence of treatment and diagnosis apply across both groups. The younger the patient at diagnosis and treatment, the greater the risk, for example, of cognitive deficits following treatments such as craniotomy and cranial irradiation and the resultant psychosocial interventions required. However, regardless of age, a patient with a brain tumour may experience impaired cognitive and functional outcomes as a result of the tumour, raised intracranial pressure and surgery to remove it.

Our immediate recommendations to survivorship researchers across the field are to: 1) always document both age at cancer diagnosis/treatment and current age in all types of survivorship research, 2) avoid merging the outcomes and needs of CCS and AYACS within the one study and where possible, conducting subgroup analyses to explore any differences, and 3) consider survivors’ developmental stage at cancer diagnosis/treatment when interpreting research findings.

Our pragmatic vision for future work focuses on 1) additional qualitative research to provide deeper, nuanced understanding of young people’s survivorship experiences, and to highlight differences and similarities between CCS and AYACS across psychosocial domains (including, but not limited to, mental health, social and sexual development and cognitive development), 2) Encouraging collaboration across sites and countries to build larger prospective research cohorts that allow examination of differences in outcomes and needs between CCS and AYACS. This approach may address some of the challenges in our field in recruiting and gathering robust data, and 3) Working towards agreement on the use of common patient-reported outcomes and on which outcomes/needs to measure, which would support building the evidence base from a quantitative perspective.

It is important to note that age at diagnosis is not yet confirmed as important predictor in large datasets which have been used in national cohort studies with CCS. Focus in these cohort studies have often been on generic psychosocial outcomes in relation to the predictive power of medical determinants. Often these large datasets lack precision and granularity of age-appropriate outcomes to uncover age at diagnosis related to specific consequences while homogeneous datasets often lack power in terms of sample size.20,21 Homogeneity around diagnosis might shed more light on the age of diagnosis in a particular group. This would advocate for larger datasets capable of robust subgroup analysis, with targeted developmentally appropriate outcome measures that can uncover possible effects of age at diagnosis. We also believe longitudinal studies might help in shedding more light on particular trajectories over time of potentially vulnerable children. In addition, qualitative work could shed light on experiences and possible differences of experience for young survivors, dependent on age at diagnosis.

Finally, the organization of care according to age at diagnosis is a barrier to a clear pathway for support of young survivors. It is important to overcome differences in treatment settings (pediatric versus adult care settings) and care for survivors, by applying key elements of transition care, such as age-adapted patient education, involvement of caregivers, a responsible coordinator, digital interventions, and the provision of a treatment summary.22 In addition, the following would aid progress in the field:

* Learning from the AYA community – bridging care between pediatrics and adult care
* Developing sustainable models of collaborative working between pediatrics and adult care
* Focusing on risk-adaptive models
* Providing additional educational opportunities
* Increasing prioritisation of survivorship research and need to follow late effects
* Engaging more fully with survivors / patients
* Exploring ‘empty’ episodes of care, and how young people engage with survivorship care
* Considering differences in health care systems
* Emphasising the importance of transition programmes
* Empowering survivors to advocate for themselves

Our hope is that these developments will, in time, enable us to truly understand the shared, and distinct, experiences of two growing groups of cancer survivors: CCS and AYACS.

**Figure 1: Distinguishing between CCS and AYACS and consequences of lack of clarity**

**Acknowledgements**

Claire Wakefield is supported by the NHMRC of Australia (APP1143767 and APP2008300).**References**

1. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Girardi F, Atun R. Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. *The Lancet Oncol*. 2019;20: 972-983.

2. Marjerrison S, Barr RD. Unmet survivorship care needs of adolescent and young adult cancer survivors. *JAMA Network Open*. 2018;1: e180350-e180350.

3. Michel G, Brinkman TM, Wakefield CE, Grootenhuis M. Psychological Outcomes, Health-Related Quality of Life, and Neurocognitive Functioning in Survivors of Childhood Cancer and Their Parents. *Pediatr Clin North Am*. 2020;67: 1103-1134.

4. Gunnes MW, Lie RT, Bjorge T, et al. Reproduction and marriage among male survivors of cancer in childhood, adolescence and young adulthood: a national cohort study. *Br J Cancer*. 2016;114: 348-356.

5. Gunnes MW, Lie RT, Bjorge T, et al. Economic independence in survivors of cancer diagnosed at a young age: A Norwegian national cohort study. *Cancer*. 2016;122: 3873-3882.

6. Brewster DH, Clark D, Hopkins L, et al. Subsequent hospitalisation experience of 5-year survivors of childhood, adolescent, and young adult cancer in Scotland: a population based, retrospective cohort study. *Br J Cancer*. 2014;110: 1342-1350.

7. Kazak AE, Derosa BW, Schwartz LA, et al. Psychological outcomes and health beliefs in adolescent and young adult survivors of childhood cancer and controls. *J Clin Oncol*. 2010;28: 2002-2007.

8. Bitsko MJ, Cohen D, Dillon R, Harvey J, Krull K, Klosky JL. Psychosocial Late Effects in Pediatric Cancer Survivors: A Report From the Children's Oncology Group. *Pediatr Blood Cancer*. 2016;63: 337-343.

9. Geiger AM, Castellino SM. Delineating the Age Ranges Used to Define Adolescents and Young Adults. *J Clin Oncol*. 2011;29: e492-e493.

10. Erikson EH. *Identity: Youth and crisis*. WW Norton & Company, 1968.

11. Erikson EH. *Childhood and Society*. Second ed. New York: Norton & Company Inc.; 1963.

12. D’Agostino NM, Edelstein K. Psychosocial challenges and resource needs of young adult cancer survivors: implications for program development. *J Psychosocial Oncol Res Prac*. 2013;31: 585-600.

13. Kadan-Lottick NS, Robison LL, Gurney JG, et al. Childhood cancer survivors' knowledge about their past diagnosis and treatment: Childhood Cancer Survivor Study. *JAMA*. 2002;287: 1832-1839.

14. Brand S, Wolfe J, Samsel C. The impact of cancer and its treatment on the growth and development of the pediatric patient. *Current Pediatric Reviews*. 2017;13: 24-33.

15. Arnett JJ, Ramos KD, Jensen LA. Ideological views in emerging adulthood: Balancing autonomy and community. *J Adult Dev*. 2001;8: 69-79.

16. Piaget J. *The theory of stages in cognitive development*. In: Green DR, Ford MP, Flamer GB, editors. Measurement and Piaget: McGraw-Hill; 1971.

17. Moore BD, 3rd. Neurocognitive outcomes in survivors of childhood cancer. *J Pediatr Psychol*. 2005;30: 51-63.

18. Krull KR, Hardy KK, Kahalley LS, Schuitema I, Kesler SR. Neurocognitive outcomes and interventions in long-term survivors of childhood cancer. *J Clin Oncol*. 2018;36: 2181.

19. Palmer SL, Armstrong C, Onar-Thomas A, et al. Processing speed, attention, and working memory after treatment for medulloblastoma: an international, prospective, and longitudinal study. *J Clin Oncol*. 2013;31: 3494.

20. Zeltzer LK, Lu Q, Leisenring W, Tsao JC, Recklitis C, Armstrong G, Mertens AC, Robison LL, Ness KK. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev*. 2008;17:435-46.

21. Prasad PK, Hardy KK, Zhang N, Edelstein K, Srivastava D, Zeltzer L, Stovall M, Seibel NL, Leisenring W, Armstrong GT, Robison LL, Krull K. Psychosocial and Neurocognitive Outcomes in Adult Survivors of Adolescent and Early Young Adult Cancer: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol*. 2015;33:2545-52.

22. Pape L, Ernst G. Health care transition from pediatric to adult care: an evidence-based guideline. *Eur J Paeds*. 2022 January