Childhood cancer: survival, treatment modalities, late effects and improvements over time

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Highlights

- Improvements in childhood cancer survival led to increasing numbers of survivors
- Childhood cancer is treated within multiinstitutional clinical trials
- Chemotherapy is the main element of therapy but irradiation is still needed in some
- Survivors are at longstanding risk of severe somatic late effects
- Survivors may face various social and socioeconomic difficulties in adulthood

Abstract

Since the 1960s, paediatric oncologists have gradually become better organised in large study groups and participation in clinical trials is today considered as the standard of care, with most children with cancer in Europe and North America being enrolled on available treatment protocols. Chemotherapy is nowadays the main element of therapy, but irradiation is still required for some patients. With the advent of multimodality therapy and supportive care, five-year cancer survival exceeds 80% in most European and North American countries today. The substantial improvements in survival led to a constantly growing population of childhood cancer survivors. Concerns regarding the risk of late effects of the intensive cancer treatment at a young age, together with increasing numbers of survivors, have directed attention towards survivorship research. Survivors of childhood cancer are at longstanding risk of various severe somatic and mental health conditions attributable to the cancer and its treatment, as well as adverse social and socioeconomic consequences, and diminished psychological well-being and quality of life. It is, however, important to stress that some survivors have no or very mild adverse health conditions. Nevertheless, joint efforts are warranted for the care and long-term follow-up of childhood cancer patients.

With this article, we provide a comprehensive overview of improvements in survival and treatment modalities over time, as well as the related somatic and mental late effects, and social and socioeconomic difficulties that these children might encounter later in life.

Introduction

Childhood cancer is a heterogeneous group of malignancies, consisting of a range of very different diseases with different patterns of occurrence (1), aetiology (2), treatment and supportive care, survival (3) and the risk of acute toxic side and late effects (4, 5). Over the past five decades, substantial advances in diagnostics, pharmacology, treatment combinations and techniques have led to large improvements in survival from childhood cancer and declining mortality rates (6, 7). Overall survival of childhood cancer has improved from 30% in the 1960s to now exceeding 80% in most high-income countries (3). However, not all children benefit equally from these improvements and outcome depends upon type of malignancy, age of clinical onset, anatomical site, stage of the disease (in solid tumor) and somatic genetic lesions. Further, survival varies substantially by region of the world, as well as within regions (3, 8, 9). The latter applies especially to resource-limited settings, and to a much lesser extent - but still measurable - to high-income countries by social and socioeconomic group (10).

Because of improving survival and lack of preventive measures to preclude the disease (2, 11), the number of childhood cancer survivors reaching adulthood is steadily increasing. This growing population, with many years of life ahead of them, has increased attention and concerns about the risk of late effects induced by cancer treatment exposures at a young age (12) and attracted great interest towards survivorship research (13-15). Survivors of childhood cancer are at risk for various somatic and mental health conditions attributable to the cancer and its treatment (4, 5) as well as adverse social and socioeconomic consequences and diminished psychological well-being and quality of life (16-19).

In this article, we provide a comprehensive overview of the developments and improvements in childhood cancer survival and treatment modalities over time, summarize the wide range of somatic and mental late effects as well as the social and socioeconomic difficulties that childhood cancer survivors may encounter later in life and highlight the need of long-term follow-up care to facilitate early detection of health problems and social support.

Survival from childhood cancer

Before 1960, childhood leukaemia, the most common type of childhood cancer, was considered a deadly, mostly incurable disease (20). Currently, 5-year population-based survival of childhood acute lymphoblastic leukaemia (ALL) exceeds 90% in some European and North American countries (8, 9).

For all childhood cancers combined, 5-year survival in Europe increased from 54% in 1978-1982 to 75% in 1993-1997 (21), and approached 80% in 2005-2007 (3). In the US, 5-year relative survival rose from 58% in 1975-1977 to 85.3% in 2009-2015 (22). Survival has, however, not increased similarly in all parts of the world: reliable population-based cancer registry data are limited or entirely lacking in many low and middle-income countries (23), but estimates suggest that survival is substantially lower compared to high-income settings (8). A simulation study estimated that 5-year survival for all childhood cancers combined was only 8.1% in Eastern Africa in 2015 (95% uncertainty interval 4.4-13.7%) (24). Further, it was estimated that in 2017, childhood cancers (0-19 years) were responsible for over 11 million years of life lost globally, with an overwhelming majority (61%) being observed in low- and low-middle income settings (25).

Irrespectively of the country's wealth and health expenditure, survival varies widely by childhood cancer type. Despite evidence suggesting that recent survival improvements were larger for acute myeloid leukaemia (AML) than for ALL in many countries (9), survival from ALL is still consistently higher than that for AML in Europe (3), the US (26), Japan (27), Australia (28), and globally (9, 24). Five-year survival exceeds 70% for AML in some high-income countries, exceeds 90% for Burkitt and Hodgkin lymphoma, retinoblastoma, and nephroblastoma, but it is still below 60% for some types of hepatic and central nervous system (CNS) tumours (3, 9, 24, 26). Large survival disparities across regions of the world are also observed for individual childhood cancer types (3, 8). Figure 1 illustrates the international disparities in survival from ALL and from brain tumours, based on population-based survival estimates from the international CONCORD-3 programme (8).

Important prognostic factors for childhood cancers can include sex and age at diagnosis as well as disease subtype, site, histology, grade, stage, and other clinical factors (29-34). Infants (<1 year) and older children (>10 years) have the poorest prognosis for all cancers (3, 9, 35) except for some embryonal tumours, for which infants have a better prognosis than older children (3, 36-38). Evidence is accumulating that not only clinical factors, but also factors indicating low socioeconomic status, are associated with worse survival even within European countries (10, 39-46), where mostly equal access to health care services, irrespective of socioeconomic background, is presumed. Cancer survival for children has also been reported to vary by race or ethnicity, mainly based on data from the US (36, 47-50). Noteably a recent mediation

analysis found that the racial or ethnic survival disparities for childhood cancer in the US were only partly explained by socioeconomic differences (51).

Treatment of children with cancer over time

Chemotherapy was introduced as a treatment for childhood leukaemia in the 1950s, but still all patients died. In an attempt to change this, a number of clinical trials introduced protocol-based combination of chemotherapy despite resistance from academia (52), and paediatric acute lymphoblastic leukaemia became the first example of cure of disseminated cancer. Since the 1960s, paediatric oncologists have organised to form large multidisciplinary study groups, and participation in clinical trials is today considered as the standard of care with most children in Europe and North America being enrolled on available protocols (53), ultimately contributing to substantial improvements in survival. The hallmark of the success of leukaemia therapy was the acceptance of proposals to categorize leukaemia by cell subtypes and morphological subgroups and to design treatment protocols accordingly.

The success of leukaemia therapy has paralleled advances in diagnostics for subgrouping, targeted therapy and risk classification. The *in vivo* response to therapy evaluated by measurable residual disease has emerged as the most important prognostic factor in leukaemia, and is used for treatment stratification in most clinical trials (34). The genetic-based characterisation of tumours has led to significant changes in classification e.g. in medulloblastoma, which was previously characterised as one homogenous malignancy, but is currently subdivided into four main groups on the basis of differences in genetic alterations, age at onset and prognosis, thereby also emphasising sub-group-tailored therapy (54).

Treatment of solid tumours has progressed from being a solely surgical approach with low survival probabilities, to the addition of radiation and later replacement by a multi-modality treatment mainly based on chemotherapy, which has resulted in significant improvements in survival. As the late effects of irradiation became evident, the number of patients receiving irradiation has been successfully reduced, e.g. in Wilms tumour patients and very young children with brain tumours, while irradiation is still essential in many other solid tumours (55). However, regional differences do exist with irradiation being used more often in North America compared to Europe (56). Importantly, newer approaches for delivery of radiation therapy, including conformal radiation, intensity modulated radiotherapy and proton therapy, have been introduced with the intent to reduce the adverse long-term effects of radiation (57). CNS

irradiation was given to most children with leukaemia in the 1970s but has gradually been replaced by chemotherapy. This change in treatment modalities has resulted in a significant decline of irradiation-induced late effects, although the overall burden of late effects remains relatively high (58, 59) (please see section somatic and mental late effects).

Modern therapy for some malignancies is very intensive and while survival has gradually improved, so has the risk of treatment-related death. There is a delicate balance between efficacy and toxicity, and it is considered that the upper limit of treatment intensity has been reached in many diseases (60). The aim of many current protocols is to identify patients, for whom therapy intensity can be reduced, and thereby the physical burden of treatment, without jeopardising survival. Thus, it is evident that collaboration on an international level is necessary to continue to build upon the major improvements already achieved in the management of childhood cancers.

There is a large inter-individual variation in the pharmacokinetic of cytostatic drugs. A few constitutional risk factors for specific toxicities are known, e.g. TPMT status during 6-mercaptopurine therapy, anthracycline-induced cardiotoxicity (61), or mitochondrial mutations leading to a high risk of deafness when exposed to aminoglycoside (62). Further studies of single nucleotide polymorphism variants increasing the susceptibility to acute and/or long-term toxicities of cancer drugs may ultimately lead to personalised precision medicine approaches for the treatment of childhood cancers.

A substantial and not quantifiable proportion of patients in resource-poor countries have limited access to diagnostics and therapy, and may not receive any therapy for economic or cultural reasons (63). If treatment is initiated, blood support as well as management of infections and nutritional problems may be a hurdle in most low-income countries. The early mortality rate has been reported to be extremely high in low-income countries compared to high-income countries (7, 64).

Somatic and mental late effects

Over the past decades, it has become increasingly evident that survivors of childhood cancer may experience, to varying degrees, a wide range of adverse health outcomes resulting from previous therapeutic exposures that can affect almost any organ or body system (65). Several comprehensive cohorts of childhood cancer survivors have been established in Europe and

North America to assess the risk of a large variety of somatic and mental late effects. Table 1-4 provide a summary of the largest and most comprehensive studies to date on somatic and mental late effects based on these childhood cancer survivor cohorts, as reported by the respective cohort investigators. Other cohorts are being established, such as the nationwide population-based French Childhood Cancer Observation Platform (CCOP) (66), which is based on the French national childhood cancer registry and includes detailed treatment information abstracted from medical records.

In general, only few studies have been able to provide a comprehensive overview of the complex and often serious somatic disease burden after childhood cancer (59, 67-73) (Table 1). Large studies from North America and the Netherlands, with comprehensive clinical examination of various chronic health conditions, have provided evidence of a substantial somatic disease burden among childhood cancer survivors (58, 59, 67, 68). Bhakta et al. found that, by age 50 years, survivors had experienced on average 17 grade 1-5 chronic health conditions including five health conditions classified as grade 3-5 (severe/disabling, life-threatening or fatal), as compared to on average nine grade 1-5 chronic health conditions in community controls (67). Additionally, large-scale population-based cohorts from the Nordic countries and Canada have assessed late effects using high quality registry-based data and provided novel evidence of consistently elevated risks of hospital contacts or visits to physicians for somatic diseases in a lifelong perspective (69-72). Among more than 21,000 5-year childhood cancer survivors from the Nordic countries, survivors were found to be twice as likely to be hospitalised and experienced longer stays in hospitals than population-based comparisons (69). In the Canadian setting, McBride et al. reported an almost 2-fold higher utilisation of outpatient visits to physicians among survivors compared to the general population (72).

Assessing temporal patterns in the risk of chronic health conditions (Table 1), Gibson et al. from the Childhood Cancer Survivor Study found that the 20-year cumulative incidence of such conditions decreased significantly over three decades from 33.2% in 1970-1079 to 27.5% in 1990-1999. Such improvements were, however, not observed across all childhood cancer types (58). Based on a clinical assessment of long-term survivors of childhood ALL treated between 1962 and 1991, Mulrooney et al. from the St. Jude Lifetime Cohort study demonstrated that despite significant changes in therapy over time, the overall cumulative burden of chronic health conditions in ALL survivors has remained high, whereas the pattern of morbidity has changed

substantially (59). It is, however, important to stress that many of the conditions driving the overall increased risk in ALL survivors were mild chronic conditions, such as growth hormone deficiency (24% vs 2% among controls) and neuropathy (e.g. peripheral sensory neuropathy: 30% vs 13% among controls).

Compared with cancer incidence in the general population, childhood cancer survivors also face an elevated risk of second malignant neoplasms (74-78) (Table 2). A Dutch study reported an overall 5-fold increased risk of second malignant neoplasms, equivalent to 20 excess cancers per 10,000 person-years (74). Three large studies with unique data deriving from the EU-funded PanCareSurFup consortium (www.pancaresurfup.eu) demonstrated a 22- and a 30-fold increased risk of subsequent primary bone cancer and soft-tissue sarcomas in five-year childhood cancer survivors, respectively (75, 77), and a four-fold increased risk of subsequent leukaemias (76) compared to population norms.

Other studies have often focused on a single health outcome or organ system (79-89) (Table 3). Compared to the general population or siblings, some of these studies reported a 4.8-fold increased risk of hospital contact for any endocrine disorder (82), an 8.5-fold increased risk of stroke among irradiated survivors (81), a 6.8-fold increased risk of respiratory mortality (86), and more frequent hearing loss among survivors of childhood cancer (87). Increasingly, research has focused on the role of genetic susceptibility in determining risk of long-term adverse outcomes (90), including recently published findings from the large EU-funded PanCareLIFE consortium (www.pancarelife.eu), indicating an increased risk of cisplatin-induced ototoxicity in carriers of specific genetic polymorphisms (ACYP2 rs1872328 variant and SLC22A2 rs316019) (88).

Beyond the high risk for somatic late effects, experiences related to the childhood cancer diagnosis itself or potential consequences of the subsequent treatment may also adversely affect the mental health of survivors (18, 19, 91, 92) (Table 4). While studies from North America and Switzerland have reassuringly reported low or similar levels of psychological distress among survivors compared to the general population (18, 19), subgroups of survivors with poor physical health conditions experience elevated psychological distress, including symptoms of depression, anxiety, and psychotic tendencies (18, 19). Elevated levels of psychological distress may contribute to the observed increased use of various antidepressants (92) and higher rates of suicide ideation among survivors (91). Moreover, two population-based register studies from

Denmark and Canada both provided evidence of greater risks of hospitalisations and mental health care visits for severe mental health disorders among childhood cancer survivors than in the general population (93, 94).

Social and socioeconomic difficulties in childhood cancer survivors

The immediate impact of a cancer diagnosis and its treatment during childhood may, apart from somatic and mental conditions, result in maladaptive coping, missed educational achievements, isolation or reduced interaction with peers, and social engagements (17, 95, 96). Moreover, experiencing a cancer during childhood, suffering from somatic or mental late effects or other adverse health conditions may also affect social and family life and diminish socioeconomic achievements during later life (16-19).

The current literature indicates that childhood cancer survivors are at increased risk of several adverse socioeconomic and social conditions compared to individuals who did not suffer from cancer during childhood (16). Several large-scale studies observed lower educational attainments in childhood cancer survivors compared to cancer-free children (97-100), although findings from Switzerland suggested rather a delay in educational achievement than a long-lasting difference (101). Empirical observations on the employment situation and occupation of childhood cancer survivors are less conclusive and varied by geographical region (16, 102). Findings from two systematic reviews and meta-analyses point towards a 1.5–2 times increased risk of unemployment in childhood cancer survivors (102, 103). Specifically, survivors in the US and Canada appear to be at greater risk of being unemployed (102), whereas observations from Europe were less consistent. Some studies found higher unemployment rates among European survivors compared to the general population (104-106), whereas others did not (100, 107-110). Both a lower educational attainment and unemployment may have a direct impact on the survivors' economical situation. Several studies found the survivors' income to be markedly lower compared to their siblings or the general population (16, 100, 106, 111, 112). Empirical knowledge on the uptake of social security benefits such as benefits referring to unemployment, sickness, disability, rehabilitation or permanent invalidity is particularly sparse but does suggest an increased uptake of such benefits in childhood cancer survivors (16). In general, survivors of CNS tumours, survivors treated with cranial radiotherapy, and those diagnosed at younger age have a higher risk of adverse socioeconomic outcomes, irrespective of cancer type, although the underlying mechanisms are not well understood (16).

Overall, childhood cancer survivors tend to leave the parental home at an older age (113, 114) and have lower rates of marriage or cohabitation (115-118) than young adults without a cancer diagnosis during childhood. Findings from Denmark showed that CNS tumour survivors, and male survivors in particular, had a lower probability of leaving the parental home in early adulthood (113). Such patterns were, however, not seen in survivors of other diagnostic groups (113). Similar findings were found in a study from the US with survivors being more than twice as likely to stay at the parental home compared to a sibling comparison group, with survivors diagnosed with a CNS tumour or leukaemia having the greatest odds (119). Findings from Europe and North America (115-118) consistently revealed lower marriage and cohabitation rates among childhood cancer survivors compared with peers. A CNS tumour diagnosis, history of cranial irradiation, and male sex appeared to be the most important predictors of not having a partner (115, 116, 118). Despite the reduced rates of marriage and cohabitation, evidence does however not support that separation or divorce is more frequent in survivors than in the general population or in sibling comparisons (116, 118, 120).

Observations on parenthood and infertility revealed that female and male childhood cancer survivors are less likely of ever parenting a child (117, 121-123). This may be a result of both biological repercussions of the childhood cancer including treatment-induced fertility problems, psychosocial consequences, difficulties in finding a partner, or concerns about the health of their future children. Impaired fertility may be caused by the oncological treatment such as radiation therapy in the pelvic area or certain chemotherapeutic drugs, especially alkylating agents, which can induce sperm alteration, ovarian failure or earlier menopause (124-127).

Perspectives

With the advent of multimodality therapy, the survival from childhood cancer has markedly improved over the past five decades (3). Reports from the US and Europe, however, indicate that the relative increase in survival for several childhood cancer subtypes has decreased during recent years (3, 8).

Over the last decades, in an effort to provide comparable population-based survival estimates to inform health policy-makers, health care professionals and scientists, a number of European (128-131) and international (8, 132-136) collaborations have been created, with only one being specifically dedicated to children with cancer (137). Survival is challenging to study due to

differences in cancer registration practices, in particular for CNS tumours with tumours of benign behavior and those without microscopic verification (8). Although stage at diagnosis is well known to influence survival, the collection of data on stage at diagnosis in population-based cancer registries is very challenging. Until recently, if at all recorded, childhood cancer stage used to be coded according to the TNM classification for adults, due to lack of childhood-specific guidelines (138). However, the recent development of guidelines for harmonising stage records in childhood cancer registries are an important step, and will enable analyses of survival according to stage in the years to come (138, 139).

With the recognition that survivors of childhood cancer were at increased risk of long-term adverse outcomes, paediatric oncology professionals have continually worked toward the goal of maximising the chance of survival, while minimising long-term toxicities. Recent studies have provided convincing support that treatment modifications have resulted in overall improved long-term outcomes and lifespan extension for many survivors of childhood cancer, although not uniformly across all types of childhood cancer (58, 140). The lower increase in survival and improvements in long-term outcomes underscore the importance of further research addressing specific types of childhood cancer.

As underlined more than 40 years ago by Dr Giulio J. D'Angio, most survivors need lifelong survivorship care (141). However, implementing follow-up care for childhood cancer has proven challenging across the globe (142). As risk-based survivorship care is complex, this might be one reason for many survivors not receiving optimal care. Another reason might be lack of harmonised evidence-based guidelines, which was met in 2010, when the International Late Effects of Childhood Cancer Guideline Harmonisation Group (IGHG; www.ighg.org) for long-term follow-up of children, adolescence, and young adult cancer survivors was initiated. This international initiative will largely contribute to standardise survivorship care across the globe and improve long-term outcomes in childhood cancer survivors in the years to come.

Based on these international guidelines for surveillance of late effects, a new EU-funded collaborative project PanCareFollowUp (www.pancarefollowup.eu), with the overall aim of improving the quality of life for survivors of childhood and adolescent cancer by bringing together evidence-based, person-centered care to clinical practice, was initiated. Four state-of-the-art clinics in Sweden, Belgium, Italy, Czech Republic are actively involving patients as partners to empower survivors and to support self-management. Experiences from

PanCareFollowUp and other international initiatives are urgently needed to further contribute to standardised and evidence-based survivorship care in other regions of the world and to ultimately improve outcomes after childhood cancer in a global context.

Continued and concerted efforts are required from researchers, clinicians and policy-makers to address the need of survivors; i.e., effective innovative treatments, financial support aiming at reducing inequalities and increasing access to standard care, expertise and clinical research as well as tailored follow-up care throughout lifespan to facilitate early detection of health problems and social support. The overall aim is to improve the health and quality of life (143), and to ensure that 'the increasing numbers of successfully treated children of today do not become the chronically ill adults of tomorrow' (141).

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References

1. Steliarova-Foucher E, Colombet M, Ries L, Hesseling P, Moreno F, Shin H, et al. International Incidence of Childhood Cancer, Volume III (electronic version) Lyon, France: International Agency for Research on Cancer; 2017 [Available from: http://iicc.iarc.fr/results/.
2. Spector LG, Pankratz N, Marcotte EL. Genetic and Nongenetic Risk Factors for Childhood Cancer. Pediatric clinics of North America. 2015;62(1):11-25.
3. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. Lancet Oncol. 2014;15(1):35-47.
4. Landier W, Armenian S, Bhatia S. Late effects of childhood cancer and its treatment. Pediatric clinics of North America. 2015;62(1):275-300.
5. Fidler MM, Reulen RC, Winter DL, Kelly J, Jenkinson HC, Skinner R, et al. Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. Bmj. 2016;354:i4351.
6. Schmiegelow K, Forestier E, Hellebostad M, Heyman M, Kristinsson J, Soderhall S, et al. Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia. Leukemia. 2010;24(2):345-54.
7. Pritchard-Jones K, Pieters R, Reaman GH, Hjorth L, Downie P, Calaminus G, et al. Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries. The Lancet Oncology. 2013;14(3):e95-e103.
8. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391(10125):1023-75.
9. Bonaventure A, Harewood R, Stiller CA, Gatta G, Clavel J, Stefan DC, et al. Worldwide comparison of survival from childhood leukaemia for 1995-2009, by subtype, age, and sex (CONCORD-2): a population-based study of individual data for 89 828 children from 198 registries in 53 countries. Lancet Haematol. 2017;4(5):e202-e17.
10. Mogensen H, Modig K, Tettamanti G, Erdmann F, Heyman M, Feychting M. Survival After Childhood Cancer-Social Inequalities in High-Income Countries. Front Oncol. 2018;8:485.
11. Erdmann F, Ghantous A, Schüz J. Environmental Agents and Childhood Cancer. 2019. p. 347-59.
12. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic Health Conditions in Adult Survivors of Childhood Cancer. N Engl J Med. 2006;2006;355:1572-82.
13. Bhatia S, Armenian SH, Armstrong GT, van Dulmen-den Broeder E, Hawkins MM, Kremer LC, et al. Collaborative Research in Childhood Cancer Survivorship: The Current Landscape. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(27):3055-64.
14. Liu L, O'Donnell P, Sullivan R, Katalinic A, Moser L, de Boer A, et al. Cancer in Europe: Death sentence or life sentence? European journal of cancer. 2016;65:150-5.
15. Hudson MM, Armenian SH, Armstrong GT, Chow EJ, Henderson TO. Optimization of Health and Extension of Lifespan Through Childhood Cancer Survivorship Research. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018:JCO2018790477.

16. Frederiksen LE, Mader L, Feychting M, Mogensen H, Madanat-Harjuoja L, Malila N, et al. Surviving childhood cancer: A systematic review of studies on risk and determinants of adverse socioeconomic outcomes. International journal of cancer Journal international du cancer. 2018.
17. Brinkman TM, Recklitis CJ, Michel G, Grootenhuis MA, Klosky K. Psychological Symptoms, Social Outcomes, Socioeconomic Attainment, and Health Behaviors Among Survivors of Childhood Cancer: Current State of the Literature. Journal of Clinical Oncology. 2018;36(21):2190-7.
18. Michel G, Rebholz CE, Von der Weid NX, Bergstraesser E, Kuehni CE. Psychological Distress in Adult Survivors of Childhood Cancer : The Swiss Childhood Cancer Survivor Study. Journal of Clinical Oncology. 2010;28(10):1740-8.
19. Brinkman TM, Zhu L, Zeltzer LK, Recklitis CJ, Kimberg C, Zhang N, et al. Longitudinal patterns of psychological distress in adult survivors of childhood cancer. British journal of cancer. 2013;109(5):1373-81.
20. de Nully Brown P, Olsen JH, Hertz H, Carstensen B, Bautz A. Trends in survival after childhood cancer in Denmark, 1943-87: a population-based study. Acta Paediatr. 1995;84(3):316-24.
21. Magnani C, Pastore G, Coebergh JW, Viscomi S, Spix C, Steliarova-Foucher E. Trends in survival after childhood cancer in Europe, 1978-1997: report from the Automated Childhood Cancer Information System project (ACCIS). European journal of cancer (Oxford, England : 1990). 2006;42(13):1981-2005.
22. <ref 000072 BRECKENKAMP J 2010.pdf>.
23. Bray F, Ferlay J, Laversanne M, Brewster DH, Gombe Mbalawa C, Kohler B, et al. Cancer Incidence in Five Continents: Inclusion criteria, highlights from Volume X and the global status of cancer registration. International journal of cancer. 2015;137(9):2060-71.
24. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Girardi F, Atun R. Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. Lancet Oncol. 2019;20(7):972-83.
25. The global burden of childhood and adolescent cancer in 2017: an analysis of the Global Burden of Disease Study 2017. Lancet Oncol. 2019;20(9):1211-25.
26. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.
27. Nakata K, Ito Y, Magadi W, Bonaventure A, Stiller CA, Katanoda K, et al. Childhood cancer incidence and survival in Japan and England: A population-based study (1993-2010). Cancer Sci. 2018;109(2):422-34.
28. Baade PD, Youlden DR, Valery PC, Hassall T, Ward L, Green AC, et al. Population-based survival estimates for childhood cancer in Australia during the period 1997-2006. British journal of cancer. 2010;103(11):1663-70.
29. Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(15):2625-34.
30. Stanulla M, Schrappe M. Treatment of childhood acute lymphoblastic leukemia. Semin Hematol. 2009;46(1):52-63.
31. Chintagumpala M, Gajjar A. Brain tumors. Pediatr Clin North Am. 2015;62(1):167-78.
32. Allen CE, Kelly KM, Bollard CM. Pediatric lymphomas and histiocytic disorders of childhood. Pediatr Clin North Am. 2015;62(1):139-65.
33. Rodriguez-Galindo C, Orbach DB, VanderVeen D. Retinoblastoma. Pediatr Clin North Am. 2015;62(1):201-23.

34. Tierens A, Bjorklund E, Siitonen S, Marquart HV, Wulff-Juergensen G, Pelliniemi TT, et al. Residual disease detected by flow cytometry is an independent predictor of survival in childhood acute myeloid leukaemia; results of the NOPHO-AML 2004 study. British journal of haematology. 2016;174(4):600-9.
35. Pulte D, Gondos A, Brenner H. Trends in 5- and 10-year survival after diagnosis with childhood hematologic malignancies in the United States, 1990-2004. J Natl Cancer Inst. 2008;100(18):1301-9.
36. Linabery AM, Ross JA. Childhood and adolescent cancer survival in the US by race and ethnicity for the diagnostic period 1975-1999. Cancer. 2008;113(9):2575-96.
37. Stiller CA, Pritchard J, Steliarova-Foucher E. Liver cancer in European children: incidence and survival, 1978-1997. Report from the Automated Childhood Cancer Information System project. European journal of cancer. 2006;42(13):2115-23.
38. Spix C, Pastore G, Sankila R, Stiller CA, Steliarova-Foucher E. Neuroblastoma incidence and survival in European children (1978-1997): report from the Automated Childhood Cancer Information System project. European journal of cancer. 2006;42(13):2081-91.
39. Gupta S, Wilejto M, Pole JD, Guttmann A, Sung L. Low socioeconomic status is associated with worse survival in children with cancer: a systematic review. PLoS One. 2014;9(2):e89482.
40. Syse A, Lyngstad TH, Kravdal O. Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study. International journal of cancer. 2012;130(8):1870-8.
41. Simony SB, Lund LW, Erdmann F, Andersen KK, Winther JF, Schuz J, et al. Effect of socioeconomic position on survival after childhood cancer in Denmark. Acta oncologica. 2016;55(6):742-50.
42. Mogensen H, Modig K, Tettamanti G, Talback M, Feychting M. Socioeconomic differences in cancer survival among Swedish children. British journal of cancer. 2016;114(1):118-24.
43. Tolkkinen A, Madanat-Harjuoja L, Taskinen M, Rantanen M, Malila N, Pitkaniemi J. Impact of parental socioeconomic factors on childhood cancer mortality: a population-based registry study. Acta Oncol. 2018;57(11):1547-55.
44. Adam M, Rueegg CS, Schmidlin K, Spoerri A, Niggli F, Grotzer M, et al. Socioeconomic disparities in childhood cancer survival in Switzerland. International journal of cancer Journal international du cancer. 2016;138(12):2856-66.
45. Sergentanis T, Dessypris N, Kanavidis P, Skalkidis I, Baka M, Polychronopoulou S, et al. Socioeconomic status, area remoteness, and survival from childhood leukemia: results from the Nationwide Registry for Childhood Hematological Malignancies in Greece. Eur J Cancer Prev. 2013;22(5):473-9.
46. Njoku K, Basta N, Mann KD, McNally RJ, Pearce MS. Socioeconomic variation in survival from childhood leukaemia in northern England, 1968-2010. British journal of cancer. 2013;108(11):2339-45.
47. Siegel DA, Li J, Ding H, Singh SD, King JB, Pollack LA. Racial and ethnic differences in survival of pediatric patients with brain and central nervous system cancer in the United States. Pediatr Blood Cancer. 2019;66(2):e27501.
48. Redaniel MT, Laudico A, Mirasol-Lumague MR, Alcasabas AP, Pulte D, Brenner H. Geographic and ethnic differences in childhood leukaemia and lymphoma survival: comparisons of Philippine residents, Asian Americans and Caucasians in the United States. British journal of cancer. 2010;103(1):149-54.

49. Tai EW, Ward KC, Bonaventure A, Siegel DA, Coleman MP. Survival among children diagnosed with acute lymphoblastic leukemia in the United States, by race and age, 2001 to 2009: Findings from the CONCORD-2 study. Cancer. 2017;123 Suppl 24:5178-89.
50. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson B, et al. Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. J Natl Cancer Inst. 2017;109(9).
51. Kehm RD, Spector LG, Poynter JN, Vock DM, Altekruse SF, Osypuk TL. Does socioeconomic status account for racial and ethnic disparities in childhood cancer survival? Cancer. 2018;124(20):4090-7.
52. Simone JV. History of the treatment of childhood ALL: a paradigm for cancer cure. Best practice & research Clinical haematology. 2006;19(2):353-9.
53. Pritchard-Jones K, Dixon-Woods M, Naafs-Wilstra M, Valsecchi MG. Improving recruitment to clinical trials for cancer in childhood. Lancet Oncol. 2008;9:392-99.
54. Northcott PA, Robinson GW, Kratz CP, Mabbott DJ, Pomeroy SL, Clifford SC, et al. Medulloblastoma. Nature reviews Disease primers. 2019;5(1):11.
55. Green DM, Kun LE, Matthay KK, Meadows AT, Meyer WH, Meyers PA, et al. Relevance of historical therapeutic approaches to the contemporary treatment of pediatric solid tumors. Pediatr Blood Cancer. 2013;60(7):1083-94.
56. Gosiengfiao Y, Reichek J, Walterhouse D. What is New in Rhabdomyosarcoma Management in Children? Pediatr Drugs. 2012;14(6):389-400.
57. Baliga S, Yock TI. Proton beam therapy in pediatric oncology. Curr Opin Pediatr. 2019;31(1):28-34.
58. Gibson TM, Mostoufi-Moab S, Stratton KL, Leisenring WM, Barnea D, Chow EJ, et al. Temporal patterns in the risk of chronic health conditions in survivors of childhood cancer diagnosed 1970–99: a report from the Childhood Cancer Survivor Study cohort. The Lancet Oncology. 2018;19(12):1590-601.
59. Mulrooney DA, Hyun G, Ness KK, Bhakta N, Pui C-H, Ehrhardt MJ, et al. The changing burden of long-term health outcomes in survivors of childhood acute lymphoblastic leukaemia: a retrospective analysis of the St Jude Lifetime Cohort Study. The Lancet Haematology. 2019;6(6):e306-e16.
60. Hasle H, Kaspers GJ. Strategies for reducing the treatment-related physical burden of childhood acute myeloid leukaemia - a review. British journal of haematology. 2017;176(2):168-78.
61. Aminkeng F, Bhavsar AP, Visscher H, Rassekh SR, Li Y, Lee JW, et al. A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer. Nature genetics. 2015;47(9):1079-84.
62. Skou AS, Tranebjaerg L, Jensen T, Hasle H. Mitochondrial 12S ribosomal RNA A1555G mutation associated with cardiomyopathy and hearing loss following high-dose chemotherapy and repeated aminoglycoside exposure. The Journal of pediatrics. 2014;164(2):413-5.
63. Erdmann F, Feychting M, Mogensen H, Schmiegelow K, Zeeb H. Social Inequalities Along the Childhood Cancer Continuum: An Overview of Evidence and a Conceptual Framework to Identify Underlying Mechanisms and Pathways. Front Public Health. 2019;7:84.
64. Njuguna F, Mostert S, Slot A, Langat S, Skiles J, Sitaresmi MN, et al. Abandonment of childhood cancer treatment in Western Kenya. Archives of disease in childhood. 2014;99(7):609-14.
65. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nature reviews Cancer. 2014;14(1):61-70.

66. Poulalhon C, Vignon L, Idbrik L, Bernier-Chastagner V, Fabre M, Schleiermacher G, et al. Data resource profile - the French Childhood Cancer Observation Platform. 2019.
67. Bhakta N, Liu Q, Ness KK, Baassiri M, Eissa H, Yeo F, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). The Lancet. 2017;390(10112):2569-82.
68. Geenen MM, Cardous-Ubbink MC, Kremer LC, Van den Bos C, Van der Pal H, Heinen RC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA. 2007;297(24):2705-15.
69. de Fine Licht S, Rugbjerg K, Gudmundsdottir T, Bonnesen TG, Asdahl PH, Holmqvist AS, et al. Long-term inpatient disease burden in the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study: A cohort study of 21,297 childhood cancer survivors. PLoS Med. 2017;14(5):e1002296.
70. Sorensen GV, Winther JF, de Fine Licht S, Andersen KK, Holmqvist AS, Madanat-Harjuoja L, et al. Long-Term Risk of Hospitalization Among Five-Year Survivors of Childhood Leukemia in the Nordic Countries. J Natl Cancer Inst. 2019;111(9):943-51.
71. Lorenzi MF, Xie L, Rogers PC, Pritchard S, Goddard K, McBride ML. Hospital-related morbidity among childhood cancer survivors in British Columbia, Canada: report of the childhood, adolescent, young adult cancer survivors (CAYACS) program. International journal of cancer. 2011;128(7):1624-31.
72. McBride ML, Lorenzi MF, Page J, Broemeling A, Spinelli JJ, Goddard K, et al. Patterns of physician follow-up among young cancer survivors. Can Fam Physician. 2011;57:482-90.
73. Berbis J, Michel G, Chastagner P, Sirvent N, Demeocq F, Plantaz D, et al. A French cohort of childhood leukemia survivors: impact of hematopoietic stem cell transplantation on health status and quality of life. Biol Blood Marrow Transplant. 2013;19(7):1065-72.
74. Teepen J, Van Leeuwen FE, Tissing WJ, Van Dulmen-den Broeder E, Van den Heuvel-Eibrink MM, Van der Pal H, et al. Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER Study Cohort: Role of chemotherapy. Journal of Clinical Oncology. 2017;35(20):2288-98.
75. Bright CJ, Hawkins MM, Winter DL, Alessi D, Allodji RS, Bagnasco F, et al. Risk of Soft-Tissue Sarcoma Among 69 460 Five-Year Survivors of Childhood Cancer in Europe. Journal of the National Cancer Institute. 2018;110(6):649-60.
76. Allodji RS, Hawkins MM, Bright CJ, Fidler-Benaoudia MM, Winter DL, Alessi D, et al. Risk of subsequent primary leukaemias among 69,460 five-year survivors of childhood cancer diagnosed from 1940 to 2008 in Europe: A cohort study within PanCareSurFup. European journal of cancer. 2019;117:71-83.
77. Fidler MM, Reulen RC, Winter DL, Allodji RS, Bagnasco F, Bardi E, et al. Risk of Subsequent Bone Cancers Among 69 460 Five-Year Survivors of Childhood and Adolescent Cancer in Europe. Journal of the National Cancer Institute. 2018;110(2).
78. Frobisher C, Glaser A, Levitt GA, Cutter DJ, Winter DL, Lancashire ER, et al. Risk stratification of childhood cancer survivors necessary for evidence-based clinical long-term follow-up. British journal of cancer. 2017;117(11):1723-31.
79. Chow EJ, Chen Y, Kremer LC, Breslow NE, Hudson MM, Armstrong GT, et al. Individual prediction of heart failure among childhood cancer survivors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(5):394-402.

80. Mansouri I, Allodji RS, Hill C, El-Fayech C, Pein F, Diallo S, et al. The role of irradiated heart and left ventricular volumes in heart failure occurrence after childhood cancer. European journal of heart failure. 2019;21(4):509-18.
81. El-Fayech C, Haddy N, Allodji RS, Veres C, Diop F, Kahlouche A, et al. Cerebrovascular Diseases in Childhood Cancer Survivors: Role of the Radiation Dose to Willis Circle Arteries. International journal of radiation oncology, biology, physics. 2017;97(2):278-86.
82. de Fine Licht S, Winther JF, Gudmundsdottir T, Holmqvist AS, Bonnesen TG, Asdahl PH, et al. Hospital contacts for endocrine disorders in Adult Life after Childhood Cancer in Scandinavia (ALiCCS): a population-based cohort study. The Lancet. 2014;383(9933):1981-9.
83. de Vathaire F, El-Fayech C, Ben Ayed FF, Haddy N, Guibout C, Winter D, et al. Radiation dose to the pancreas and risk of diabetes mellitus in childhood cancer survivors: a retrospective cohort study. The Lancet Oncology. 2012;13(10):1002-10.
84. Oudin C, Berbis J, Bertrand Y, Vercasson C, Thomas F, Chastagner P, et al. Prevalence and characteristics of metabolic syndrome in adults from the French childhood leukemia survivors' cohort: a comparison with controls from the French population. Haematologica. 2018;103(4):645-54.
85. Kasteler R, Weiss A, Schindler M, Sommer G, Latzin P, von der Weid NX, et al. Long-term pulmonary disease among Swiss childhood cancer survivors. Pediatric blood & cancer. 2018;65(1).
86. Fidler MM, Reulen RC, Bright CJ, Henson KE, Kelly JS, Jenney M, et al. Respiratory mortality of childhood, adolescent and young adult cancer survivors. Thorax. 2018;73:959-68.
87. Weiss A, Sommer G, Kasteler R, Scheinemann K, Grotzer M, Kompis M, et al. Long-term auditory complications after childhood cancer: A report from the Swiss Childhood Cancer Survivor Study. Pediatric blood & cancer. 2017;64(2):364-73.
88. Clemens E, Broer L, Langer T, Uitterlinden AG, de Vries ACH, van Grotel M, et al. Genetic variation of cisplatin-induced ototoxicity in non-cranial-irradiated pediatric patients using a candidate gene approach: The International PanCareLIFE Study. The pharmacogenomics journal. 2019.
89. Reulen RC, Bright CJ, Winter DL, Fidler MM, Wong K, Guha J, et al. Pregnancy and Labor Complications in Female Survivors of Childhood Cancer: The British Childhood Cancer Survivor Study. Journal of the National Cancer Institute. 2017;109(11).
90. Bhatia S. Role of genetic susceptibility in development of treatment-related adverse outcomes in cancer survivors. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2011;20(10):2048-67.
91. Recklitis CJ, Diller LR, Li X, Najita J, Robison LL, Zeltzer L. Suicide ideation in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(4):655-61.
92. Deyell RJ, Lorenzi M, Ma S, Rassekh SR, Collet JP, Spinelli JJ, et al. Antidepressant use among survivors of childhood, adolescent and young adult cancer: a report of the Childhood, Adolescent and Young Adult Cancer Survivor (CAYACS) Research Program. Pediatr Blood Cancer. 2013;60(5):816-22.
93. Nathan PC, Nachman A, Sutradhar R, Kurdyak P, Pole JD, Lau C, et al. Adverse mental health outcomes in a population-based cohort of survivors of childhood cancer. Cancer. 2018;124(9):2045-57.

94. Lund LW, Winther JF, Dalton SO, Cederkvist L, Jeppesen P, Deltour I, et al. Hospital contact for mental disorders in survivors of childhood cancer and their siblings in Denmark: a population-based cohort study. The Lancet Oncology. 2013;14(10):971-80.
95. Gurney JG, Krull KR, Kadan-Lottick N, Nicholson HS, Nathan PC, Zebrack B, et al. Social outcomes in the Childhood Cancer Survivor Study cohort. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(14):2390-5.
96. Barrera M, Shaw AK, Speechley KN, Maunsell E, Pogany L. Educational and social late effects of childhood cancer and related clinical, personal, and familial characteristics. Cancer. 2005;104(8):1751-60.
97. Lancashire ER, Frobisher C, Reulen RC, Winter DL, Glaser A, Hawkins MM. Educational Attainment Among Adult Survivors of Childhood Cancer in Great Britain: A Population-Based Cohort Study. Journal of the National Cancer Institute. 2010;102(4):254-70.
98. Ghaderi S, Engeland A, Gunnes MW, Moster D, Ruud E, Syse A, et al. Educational attainment among long-term survivors of cancer in childhood and adolescence: a Norwegian population-based cohort study. J Cancer Surviv. 2016;10(1):87-95.
99. Koch SV, Kejs AM, Engholm G, Johansen C, Schmiegelow K. Educational attainment among survivors of childhood cancer: a population-based cohort study in Denmark. British journal of cancer. 2004;91(5):923-8.
100. Ahomaki R, Harila-Saari A, Matomaki J, Lahteenmaki PM. Non-graduation after comprehensive school, and early retirement but not unemployment are prominent in childhood cancer survivors-a Finnish registry-based study. J Cancer Surviv. 2017;11(2):284-94.
101. Kuehni CE, Strippoli MP, Rueegg CS, Rebholz CE, Bergstraesser E, Grotzer M, et al. Educational achievement in Swiss childhood cancer survivors compared with the general population. Cancer. 2012;118(5):1439-49.
102. Mader L, Michel G, Roser K. Unemployment Following Childhood Cancer. Dtsch Arztebl Int. 2017;114(47):805-12.
103. de Boer AG, Verbeek JH, van Dijk FJ. Adult survivors of childhood cancer and unemployment: A metaanalysis. Cancer. 2006;107(1):1-11.
104. Maule M, Zugna D, Migliore E, Alessi D, Merletti F, Onorati R, et al. Surviving a childhood cancer: impact on education and employment. Eur J Cancer Prev. 2016.
105. Frobisher C, Lancashire ER, Jenkinson H, Winter DL, Kelly J, Reulen RC, et al. Employment status and occupational level of adult survivors of childhood cancer in Great Britain: The British childhood cancer survivor study. International Journal of Cancer. 2017;140(12):2678-92.
106. Gunnes MW, Lie RT, Bjørge T, Syse A, Ruud E, Wesenberg F, et al. Economic independence in survivors of cancer diagnosed at a young age: A Norwegian national cohort study. Cancer. 2016;122(24):3873-82.
107. Dieluweit U, Debatin KM, Grabow D, Kaatsch P, Peter R, Seitz DC, et al. Educational and vocational achievement among long-term survivors of adolescent cancer in Germany. Pediatric blood & cancer. 2011;56(3):432-8.
108. Boman KK, Lindblad F, Hjern A. Long-term outcomes of childhood cancer survivors in Sweden: a population-based study of education, employment, and income. Cancer. 2010;116(5):1385-91.
109. Dumas A, Berger C, Auquier P, Michel G, Fresneau B, Setcheou Allodji R, et al. Educational and occupational outcomes of childhood cancer survivors 30 years after diagnosis: a French cohort study. British journal of cancer. 2016;114(9):1060-8.

110. Mader L, Vetsch J, Christen S, Baenziger J, Roser K, Dehler S, et al. Education, employment and marriage in long-term survivors of teenage and young adult cancer compared with healthy controls. Swiss Med Wkly. 2017;147:w14419.
111. Wengenroth L, Sommer G, Schindler M, Spycher BD, von der Weid NX, Stutz-Grunder E, et al. Income in Adult Survivors of Childhood Cancer. PLoS One. 2016;11(5):e0155546.
112. Teckle P, Peacock S, McBride ML, Bentley C, Goddard K, Rogers P. Long-term effects of cancer on earnings of childhood, adolescent and young adult cancer survivors - a population-based study from British Columbia, Canada. BMC Health Serv Res. 2018;18(1):826.
113. Koch SV, Kejs AM, Engholm G, Moller H, Johansen C, Schmiegelow K. Leaving home after cancer in childhood: a measure of social independence in early adulthood. Pediatric blood & cancer. 2006;47(1):61-70.
114. Langeveld NE, Ubbink MC, Last BF, Grootenhuis MA, Voûte PA, De Haan RJ. Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. Psycho-oncology. 2003;12(3):213-25.
115. Wengenroth L, Rueegg CS, Michel G, Essig S, Ammann RA, Bergstraesser E, et al. Life partnerships in childhood cancer survivors, their siblings, and the general population. Pediatric blood & cancer. 2014;61(3):538-45.
116. Janson C, Leisenring W, Cox C, Termuhlen AM, Mertens AC, Whitton JA, et al. Predictors of marriage and divorce in adult survivors of childhood cancers: a report from the Childhood Cancer Survivor Study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2009;18(10):2626-35.
117. Gunnes MW, Lie RT, Bjorge T, Ghaderi S, Ruud E, Syse A, et al. Reproduction and marriage among male survivors of cancer in childhood, adolescence and young adulthood: a national cohort study. British journal of cancer. 2016;114(3):348-56.
118. Koch SV, Kejs A, Engholm G, Møller H, Johansen C, Schmiegelow K. Marriage and divorce among childhood cancer survivors. Journal of Pediatric Hematology/ Oncology. 2011;33(7):500-5.
119. Kunin-Batson A, Kadan-Lottick N, Zhu L, Cox C, Bordes-Edgar V, Srivastava DK, et al. Predictors of independent living status in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Pediatric blood & cancer. 2011;57(7):1197-203.
120. Frobisher C, Lancashire ER, Winter DL, Taylor AJ, Reulen RC, Hawkins MM, et al. Long-term population-based divorce rates among adult survivors of childhood cancer in Britain. Pediatric blood & cancer. 2010;54(1):116-22.
121. Madanat LM, Malila N, Dyba T, Hakulinen T, Sankila R, Boice JD, Jr., et al. Probability of parenthood after early onset cancer: a population-based study. International journal of cancer Journal international du cancer. 2008;123(12):2891-8.
122. Reulen RC, Zeegers M, Wallace WHB, al E. Pregnancy outcomes among adult survivors of childhood cancer in the British Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers. 2009;18(8):2239–47.
123. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(16):2677-85.
124. Byrne J, Fears TR, Mills JL, Zeltzer LK, Sklar C, Meadows AT, et al. Fertility of long-term male survivors of acute lymphoblastic leukemia diagnosed during childhood. Pediatr Blood Cancer. 2004;42(4):364-72.

125. Reinmuth S, Hohmann C, Rendtorff R, Balcerek M, Holzhausen S, Muller A, et al. Impact of chemotherapy and radiotherapy in childhood on fertility in adulthood: the FeCt-survey of childhood cancer survivors in Germany. Journal of cancer research and clinical oncology. 2013;139(12):2071-8.
126. Green DM, Zhu L, Wang M, Chemaitilly W, Srivastava D, Kutteh WH, et al. Effect of cranial irradiation on sperm concentration of adult survivors of childhood acute lymphoblastic leukemia: a report from the St. Jude Lifetime Cohort Studydagger. Human reproduction. 2017;32(6):1192-201.
127. Kenney LB, Antal Z, Ginsberg JP, Hoppe BS, Bober SL, Yu RN, et al. Improving Male Reproductive Health After Childhood,
Adolescent, and Young Adult Cancer: Progress and Future
Directions for Survivorship Research. J Clin Oncol. 2018;36.
128. Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Estève J, editors. Survival of Cancer Patients in Europe: The EUROCARE Study. Lyon, France: IARC Scientific Publication; 1995.
129. Marcos-Gragera R, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Maynadie M, et al. Survival of European patients diagnosed with lymphoid neoplasms in 2000-2002: results of the HAEMACARE project. Haematologica. 2011;96(5):720-8.
130. Maynadie M, De Angelis R, Marcos-Gragera R, Visser O, Allemani C, Tereanu C, et al. Survival of European patients diagnosed with myeloid malignancies: a HAEMACARE study. Haematologica. 2013;98(2):230-8.
131. Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, et al. Rare cancers are not so rare: the rare cancer burden in Europe. European journal of cancer (Oxford, England : 1990). 2011;47(17):2493-511.
132. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. Lancet. 2011;377(9760):127-38.
133. Arnold M, Rutherford MJ, Bardot A, Ferlay J, Andersson TM, Myklebust TA, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study. Lancet Oncol. 2019.
134. Sankaranarayanan R, Swaminathan R, Lucas E, editors. Cancer Survival in Africa, Asia, the Caribbean and Central America. Lyon, France: International Agency for Research on Cancer, World Health Organization; 2011.
135. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol. 2008;9(8):730-56.
136. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet. 2015;385(9972):977-1010.
137. Steliarova-Foucher E, Stiller C, Kaatsch P, Berrino F, Coebergh JW, Lacour B, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. Lancet. 2004;364(9451):2097-105.
138. Gupta S, Aitken JF, Bartels U, Brierley J, Dolendo M, Friedrich P, et al. Paediatric cancer stage in population-based cancer registries: the Toronto consensus principles and guidelines. Lancet Oncol. 2016;17(4):e163-e72.
139. Youlden DR, Gupta S, Frazier AL, Moore AS, Baade PD, Valery PC, et al. Stage at diagnosis for children with blood cancers in Australia: Application of the Toronto

Paediatric Cancer Stage Guidelines in a population-based national childhood cancer registry. Pediatr Blood Cancer. 2019;66(6):e27683.
140. Armstrong GT, Chen Y, Yasui Y, Leisenring W, Gibson TM, Mertens AC, et al. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. N Engl J Med. 2016;374(9):833-42.
141. D'Angio GJ. Pediatric cancer in perspective: cure is not enough. Cancer. 1975;35:pp. 866-70.
142. Tonorezos ES, Barnea D, Cohn RJ, al. e. Models of care for survivors of childhood cancer from across the globe: advancing survivorship care in the next decade. J Clin Oncol. 2018;36:pp. 2223-30.
143. Vassal G, Schrappe M, Pritchard-Jones K, Arnold F, Basset L, Biondi A, et al. The SIOPE strategic plan: A European cancer plan for children and adolescents. Journal of Cancer Policy. 2016;8:17-32.

List of Tables and Figures

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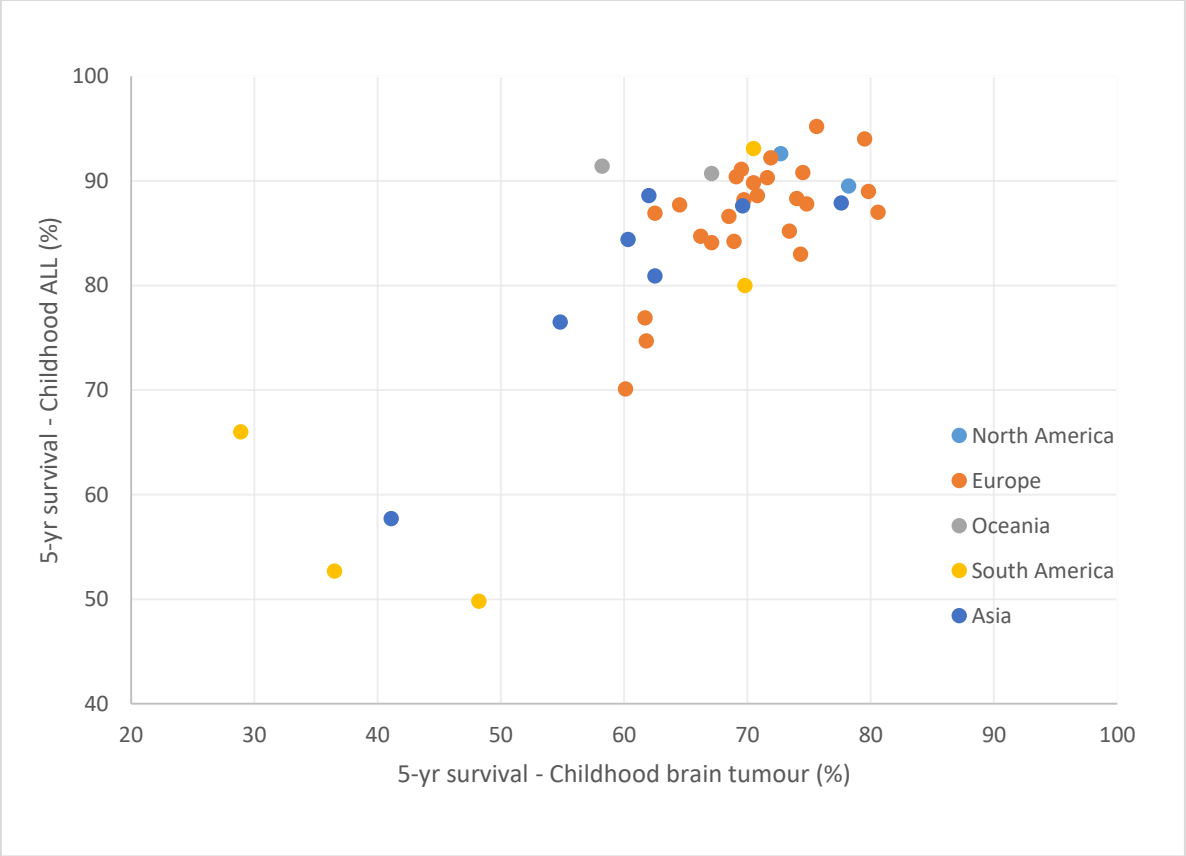

Figure 1: Distribution of worldwide 5-year age-standardised net survival estimates (%) from the CONCORD-3 study, for children diagnosed with childhood acute lymphoblastic leukaemia (ALL) and childhood brain tumours during 2010-2014. Data from CONCORD-3 (Allemani et al. 2018, Lancet) (8). Only reliable age-standardised net survival estimates are displayed, where available for childhood brain tumours and ALL. Some estimates are based on national coverage, while others are based on regional data. The x-axis is represented for 20%-100%, and y-axis for 40%-100%.

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Table 1: Summary of the largest and most comprehensive studies on somatic disease burden based on childhood cancer survivor cohorts in Europe and North America, as reported by the respective cohort investigators..

Ref.	Research cohort	Setting and childhood cancer population	No. of survivors and cancer type	Comparison cohort	Outcome ascertain-ment	Cancer treatment	Outcome measures	Key findings
Bhakta N, 2017. (1)	St. Jude Lifetime Cohort Study	Institution-based cohort of childhood cancer survivors ≥10 years from diagnosis and ≥18 years of age.	5522 survivors of all forms of childhood cancer.	272 age-, sex- and race-matched community controls.	Clinical Assessment	All cancer therapy was abstracted from medical records, including cumulative doses of individual chemotherapeutic agents. Radiation records were used to calculate region-specific radiation exposure.	168 specific chronic health conditions were graded for severity using the CTCAE criteria.	By age 50, survivors had experienced, on average 17.1 (95% CI 16.2-18.1) grade 1-5 chronic health condition, of which 4.7 (4.6-4.9) were grade 3-5. The cumulative burden in survivors was significantly greater than in community controls ($p<0.0001$). Cumulative burden of chronic health conditions at age 50 years was highest in survivors of CNS malignancies and lowest in survivors of germ cell tumours.
Mulrooney DA, 2019. (2)	St. Jude Lifetime Cohort Study	Institution-based cohort of survivors of childhood acute lymphoblastic leukaemia ≥10 years from diagnosis and ≥18 years of age.	980 survivors of childhood acute lymphoblastic leukaemia.	272 age-, sex- and race-matched community controls.	Clinical Assessment	All cancer therapy was abstracted from medical records, including cumulative doses of individual chemotherapeutic agents. Radiation records were used to calculate region-specific radiation exposure.	168 specific chronic health conditions were graded for severity using CTCAE criteria.	By age 30, survivors had experienced, on average 5.4 chronic health conditions, including 3.2 graded as moderate, severe or life-threatening. Survivors had more growth hormone deficiency, hypogonadism, and neuropathy than controls. Elimination of cranial radiation from more recent treatment protocols was associated with a higher cumulative burden for musculosketetal and endocrine disorders.

Gibson TM, 2018. (3)	Childhood Cancer Survivor Study (CCSS)	Multi-institutional cohort of 5-year survivors of common childhood cancers diagnosed in 1970-1999 before the age of 21 years.	23,601 survivors of leukaemia, CNS malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumour, neuroblastoma, soft tissue sarcoma and bone malignancy.	5051 siblings.	Questionnaire-based	All cancer therapy was abstracted from medical records, including cumulative doses of individual chemotherapeutic agents. Radiation records were used to calculate region-specific radiation exposure.	Selected chronic health conditions were graded for severity using CTCAE criteria.	20 year cumulative incidence of at least one grade 3-5 condition decreased in more recent treatment eras (33.2% in 1970s to 27.5% in 1990s), which was higher than for siblings (4.6%). Declines in cumulative incidence by treatment era were noted for endocrinopathies, subsequent malignant neoplasms, musculoskeletal conditions and gastrointestinal conditions.
Geenen MM, 2007. (4)	The Dutch Childhood Oncology Group – Long-Term Effects After Childhood Cancer (DCOG LATER)	Nationwide institution-based cohort of 5-year cancer survivors diagnosed in 1966-1996 before the age of 18 years.	1362 survivors of all cancers.	Within cohort comparison	Clinical Assessment	Treatment information were abstracted from EKZ/AMC and included information on treatment modality combinations, type of chemotherapy and region-specific radiotherapy.	Adverse events (acute and chronic conditions) graded for severity using CTCAE criteria.	74.5% of survivors had at least one adverse event and 24.6% had five or more adverse events. 40% of survivors had one or more severe or life-threatening or disabling event. Highest or most severe burden of adverse events was observed most often among survivors receiving radiotherapy only (55%), and among survivors of bone tumours (64%).
de Fine Licht S, 2017. (5)	Adult Life after Childhood Cancer in Scandinavia (ALiCCS)	Population-based cohort of 5-year childhood cancer survivors from Denmark, Finland, Iceland and Sweden diagnosed in 1943-2008	21,297 survivors of all childhood cancers.	152,231 randomly selected population comparisons matched on sex, age, year, and country.	Registry-based	No treatment information assessed.	In-patient hospital contacts for somatic diseases.	Survivors' risk of a first hospitalisation for any somatic disease (excluding cancer re-occurrences) was 2-fold compared to the general population (RR: 1.95, 95% 1.91-1.97), yielding an AER of 3.07 (95% CI: 2.98-3.16) per 100,000 person-years. Most common reasons were diseases of the nervous system, endocrine system, digestive organs, and respiratory system. Survivors spent on average

		before 21 years of age.						five times as many days in hospital as comparisons.
Sørensen GV, 2019. (6)	Adult Life after Childhood Cancer in Scandinavia (ALiCCS)	Population-based cohort of 5-year childhood cancer survivors from Denmark, Finland, Iceland and Sweden diagnosed in 1970-2008 before 21 years of age.	4003 survivors of childhood leukaemia.	129,828 randomly selected population comparisons matched on sex, age, and country.	Registry-based	No treatment information assessed.	In-patient hospital contacts for somatic diseases.	Leukaemia survivors were twice as likely to experience a first time hospital admission for a somatic disorder than the general population (RR. 2.08, 95% CI: 1.96-2.20), which remained increased beyond 20 years after leukaemia diagnosis. AER of leukaemia survivors was 32.4 per 1000 person-years (95% CI: 28.9-35-9). Survivors of CML had the largest absolute and relative risk of hospitalisation compared to the general population.
Lorenzi MF. 2011. (7)	Childhood, adolescent, young adult cancer survivors (CAYACS)	Population-based 5-year survivors of childhood cancer diagnosed in 1981-1995 before 20 years of age.	1374 survivors of all childhood cancers.	13,740 randomly selected population controls frequency-matched to cases by gender and birth year.	Registry-based	Treatment data (including primary treatment modality combinations, relapse and second cancer on yes/no levels) abstracted from medical records.	Morbidities requiring inpatient hospitalisations and scored according to severity using the CTCAE criteria.	Survivors were at higher risk of least one hospital-related morbidity than comparisons (41% vs. 17%, RR: 4.1, 95% CI: 3.7-4.5), with highest excess risk for neoplasm (including relapse or second cancer), blood disorders, and diseases of the nervous system. CNS tumour survivors were at highest excess risk of multiple morbidities. Morbidity was elevated for any combination of treatment, and highest for combination of radiation, chemotherapy and surgery (RR: 7.1, 95% CI: 5.5-9.0).
McBride ML. 2011. (8)	Childhood, adolescent, young adult cancer survivors (CAYACS)	Population-based 5-year survivors of childhood cancer diagnosed in 1970-1992 before 20 years of age.	1157 survivors of all childhood cancers.	11,570 randomly selected population controls frequency-matched to cases by	Registry-based (claim files of provincial health insurance)	Treatment data (including primary treatment modality combinations, relapse and second cancer on	Outpatient physician visits (including visits to oncologist) and utilisation of	During the 3-year follow-up period, 97% of survivors visited at least one physician, compared with 50% in the general population. Survivors were more likely to visit a general practitioner (excluding oncologists) at least 10 times (RR: 2.23, 95% CI: 2.0-2.4) and were more likely to visit a specialist as an expected result of known late effects (RR: 2.57, 95% CI

				gender and birth year.		yes/no levels) abstracted from medical records.	physician services in 1998-2000.	2.4 to 2.8). Survivors receiving combinations of treatment modalities utilised physicians and specialists more than survivors treated with surgery only.
Berbis J. 2013. (9)	French Childhood Cancer Survivor Study for Leukaemia (LEA)	Institution-based cohort of children diagnosed with acute childhood leukaemia below the age of 18 years and survived at least 24/48 months.	256 survivors of acute childhood leukaemia who underwent HSCT.	Within cohort comparison of patients treated without HSCT + HQoL mean scores were compared with age- and sex-matched French control subjects.	Clinical assessment (late effects) and questionnaire (HQoL).	Detailed history of treatment exposures were assessed from medical records with special emphasis on anthracycline cumulative dose, alkylating agents, steroids, use of radiotherapy and HSCT.	Physical late effects.	The risk of at least one late effect was 5-fold increased (95% CI. 3.0-8.6) among transplanted survivors than non-transplanted survivors. Compared with French normative data, survivors reported lower HQoL scores on mental health, but no difference on physical health.

AER; Absolute excess risk, ALL; Acute lymphoblastic leukaemia, AML; Acute myeloid leukaemia, CML; Chronic myeloid leukaemia, CTCAE; Common Terminology Criteria for Adverse Events, CNS; Central nervous system, GSI; Global severity index, HSCT; hematopoietic stem cell transplantation, HQoL; Health-related quality of life, ICD; International classification of diseases, NCSI; National Cancer Survivorship Initiative, OR; Odds ratio, O/E; Observed/expected, RR; Risk ratio, SIR; Standardised incidence ratio, SMR; Standardised mortality ratio, SPN; Subsequent primary neoplasm

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Table 2: Summary of the largest and most comprehensive studies on the risk of second malignant neoplasms based on childhood cancer survivor cohorts in Europe and North America, as reported by the respective cohort investigators.

Ref.	Research cohort	Setting and childhood cancer population	No. of survivors and cancer type	Comparison cohort	Outcome ascertain-ment	Cancer treatment	Outcome measures	Key findings
Teepen JC, 2017. (10)	The Dutch Childhood Oncology Group – Long-Term Effects After Childhood Cancer (DCOG LATER)	Nationwide institution-based cohort of 5-year cancer survivors diagnosed in 1963-2001 before the age of 18 years.	6165 survivors of all cancers.	Within cohort comparison and normative data of expected cancer incidence adjusted for overall mortality in the general population	Linkage between registries and medical records	Treatment information abstracted from EKZ/AMC, including information on dose, field and boost/surdosage for radiotherapy, and drug name, cumulative dose and start and end date for chemotherapy.	Second malignant neoplasm (SMN).	Survivors had an increased risk of any SMN compared with cancer incidence in the general population (SIR: 5.2, 95% CI: 4.6-5.8), with 20.3 excess cancers per 10,000 person-years. Treatment with doxorubicin increased the risk of subsequent solid cancers and breast cancer, whereas treatment with cyclophosphamide increased the risk of subsequent sarcomas.
Frobisher C, 2017. (11)	British Childhood Cancer Survivor Study (BCCSS)	Population-based cohort of 5-year cancer survivors diagnosed in 1940-1991 before the age of 15 years.	17,981 survivors of all types of cancer.	Population normative data of England and Wales.	Questionnaire-based	Information on exposure to initial radiation, surgery and chemotherapy (yes/no/no record). For ALL survivors treated within one of the national Medical Research Council randomised trials, specific information on cranial radiation dose was also available.	Subsequent primary neoplasms (SPNs), non-neoplastic deaths, and non-fatal non-neoplastic conditions by NCSI levels 1-3 of clinical follow-up care.	By 45 years from diagnosis, overall cumulative risk of any SPN, non-neoplastic death, or non-fatal non-neoplastic condition among survivors of NCSI level 1, 2 or 3 were 21%, 45% and 69%. For SPNs and non-neoplastic deaths, the excess risk also increased with increasing NCSI levels.

Bright CJ, 2018. (12)	PanCareSurFup Consortium*	Population- and institution-based pooled data from 13 European cohorts of five-year survivors diagnosed before age 20 years in 1940-2008.	69,460 survivors of all cancers (excluding Langerhans cell histiocytosis, myelodysplastic syndromes, chronic myeloproliferative and lymphoproliferative diseases).	Population normative data; Finnish soft-tissue incidence rates used for comparison in all Nordic countries, and UK incidence rates used for all other countries.	Mix of registries, follow-up clinics, questionnaires and available medical records.	Site of the soft-tissue sarcoma and previous radiotherapy fields was obtained from medical records.	Subsequent primary soft-tissue sarcoma.	Survivors had significantly higher risk of soft-tissue sarcoma than expected (standardised incidence ratio (SIR): 29.9, 95% CI: 23.7-37.2), with highest risk for malignant peripheral nerve sheath tumours, leiomyosarcomas and fibromatous neoplasms. AER for all soft-tissue sarcomas were low at all years from diagnosis (AER: <1 per 10,000 person-years) except for leiomyosarcoma following retinoblastoma (AER: 52.7 (95% CI: 20.0-85.5) per 10,000 person-years) among patients who had survived at least 45 years from retinoblastoma diagnosis.
Allodji RS, 2019. (13)	PanCareSurFup Consortium*	Population- and institution-based pooled data from 13 European cohorts of five-year survivors diagnosed before age 20 years in 1940-2008.	69,460 survivors of all cancers (excluding Langerhans cell histiocytosis, myelodysplastic syndromes, chronic myeloproliferative and lymphoproliferative diseases).	Population normative data; Finnish leukaemia incidence rates used for comparison in all Nordic countries, and UK incidence rates used for all other countries.	Mix of registries, follow-up clinics, questionnaires and available medical records.	No treatment information assessed.	Subsequent primary leukaemias.	Survivors had a four-fold increased risk of subsequent primary leukaemia than expected (SIR: 3.7, 95% CI: 3.1-4.5) with AER of 7.5 (95% CI: 6.0-9.2) per 100,000 person-years. The risk remained significantly elevated beyond 20 years from first primary cancer diagnosis (SIR: 2.4, 95% CI: 1.6-3.4).

Fidler MM, 2018. (14)	PanCareSurFup Consortium*	Population- and institution-based pooled data from 13 European cohorts of five-year survivors diagnosed before age 20 years in 1940-2008.	69,460 survivors of all cancers (excluding Langerhans cell histiocytosis, myelodysplastic syndromes, chronic myeloproliferative and lymphoproliferative diseases).	Population normative data; Italian normative data was used for Hungary and Slovenia, whereas Danish normative data was used for Finland, Norway and Sweden.	Mix of registries, follow-up clinics, questionnaires, medical records and hospital data, and national mortality records.	No treatment information assessed.	Subsequent bone cancers.	Survivors had a 22-fold increased risk of subsequent primary bone cancer than expected (SIR: 21.7, 95% CI: 19.0-24.6). Survivors had an AER of 2.0 (95% CI: 1.7-2.3) per 10,000 person-years with greatest risk among survivors of retinoblastoma, bone sarcoma, and soft-tissue sarcoma. AER declined linearly with both years since diagnosis and attained age (all $p<0.05$). Beyond 40 years from diagnosis and beyond 40 years of attained age, the AER was at most 0.45 per 10,000 person-years.

AER; Absolute excess risk, ALL; Acute lymphoblastic leukaemia, AML; Acute myeloid leukaemia, CML; Chronic myeloid leukaemia, CTCAE; Common Terminology Criteria for Adverse Events, CNS; Central nervous system, GSI; Global severity index, HSCT; hematopoietic stem cell transplantation, HQoL; Health-related quality of life, ICD; International classification of diseases, NCSI; National Cancer Survivorship Initiative, OR; Odds ratio, O/E; Observed/expected, RR; Risk ratio, SIR; Standardised incidence ratio, SMR; Standardised mortality ratio, SPN; Subsequent primary neoplasm

*PanCareSurFup was an EU-funded consortium active from 2011-2017, but more publications are expected in the years to come. http://www.pancaresurfup.eu/

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Table 3: Summary of the largest and most comprehensive studies on single health outcome or organ-specific late effects based on childhood cancer survivor cohorts in Europe and North America, as reported by the respective cohort investigators.

Ref.	Research cohort	Setting and childhood cancer population	No. of survivors and cancer type	Comparison cohort	Outcome ascertain-ment	Cancer treatment	Outcome measures	Key findings
Chow EJ, 2015. (15)	Childhood Cancer Survivor Study (CCSS) - Collaboration between CCSS and DCOG LATER research groups	Multi-institutional cohort of 5-year survivors of common childhood cancers diagnosed in 1970-1986 before the age of 21 years, and free of significant cardiovascular disease within 5 years of their initial cancer diagnosis	13,060 survivors of leukaemia, CNS malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumour, neuroblastoma, soft tissue sarcoma and bone malignancy.	4023 siblings, and an additional 3421 survivors from the Dutch Childhood Cancer Registry of the Emma Children's Hospital/Academic Medical Center (EKZ/AMC) were used to validate the CCSS predictions.	Questionnaire-based and linkage to the National Death Index	Information on chemotherapy (agent and dose), surgery and radiotherapy (region-specific and dose-specific) abstracted from medical records.	Risk scores of congestive heart failure (i.e. requiring medications or heart transplantation or leading to death).	Low, moderate and high-risk groups for cumulative incidence of heart failure among survivors at age 40 years were predicted to be 0.5%, 2.4%, and 11.7%, respectively. In comparison, siblings had a cumulatice incidence of 0.3%. The relative risk of heart failure among survivors compared to siblings were only minimally increased for the low-risk group ($p>0.05$) but statistically significantly elevated for the moderate-risk and high-risk groups ($p<0.01$). When the CCSS results were compared with the external cohort of EKZ/AMC, similar risk predictors were obtained.
de Fine Licht S, 2014. (16)	Adult Life after Childhood Cancer in Scandinavia (ALiCCS)	Population-based cohort of 1-year childhood cancer survivors from Denmark, Finland, Iceland, Norway and Sweden diagnosed in 1943-2008	31,723 survivors of all childhood cancers.	211,261 randomly selected population comparisons matched on sex, age, and country.	Registry-based	No treatment information assessed.	Hospital contacts for endocrine disorders.	Survivors had an overall 4.8-fold (95% CI: 4.6-5.0) increased risk of hospital contact for any endocrine disorder, equivalent to AER of about 1000 per 100,000 person-years before 20 years of age, and 400 per 100,000 person-years during the remaining lifetime. Survivors of leukaemia, CNS tumours and Hodgkin's lymphoma were at highest risk. Among the endocrine disorders investigated, pituitary

		before 21 years of age.						hypofunction predominated, representing 25% of all endocrine disorders.
Kasteler R, 2017. (17)	Swiss Childhood Cancer Survivor Study (SCCSS)	Population-based cohort of 5-year cancer survivors aged ≥16 years at survey and diagnosed in 1976-2005 at age <21 years.	1894 survivors of leukaemia, lymphoma, CNS tumours, malignant solid tumours, or Langerhans cell histiocytosis.	731 siblings.	Questionnaire-based	Information on chemotherapeutic agent, thoracic surgery (yes/no), radiotherapy and doses to the thorax (no radiation, 1-19 Gy, 20-39 Gy, ≥40 Gy), and HSCT (autologous, allogeneic, or no HSCT) from abstracted treatment protocols.	Pulmonary disease (pneumonia, chest wall abnormalities, lung fibrosis, emphysema).	After 35 years of follow-up, the cumulative incidence of any pulmonary disease was 21%. Survivors had an increased risk of pulmonary disease compared to siblings, especially pneumonia (p=0.020) and chest wall abnormalities (p=0.003). Risk factors for pneumonia were treatment with busulfan, whereas thoracic surgery was associated with risk of chest wall abnormalities and lung fibrosis.
Weiss A, 2016. (18)	Swiss Childhood Cancer Survivor Study (SCCSS)	Population-based cohort of 5-year cancer survivors diagnosed in 1976-2005 at age ≤16 years.	2061 survivors of leukaemia, lymphoma, CNS tumours, malignant solid tumours, or Langerhans cell histiocytosis.	864 siblings.	Questionnaire-based	Information on chemotherapy (yes/no, agent), radiotherapy (yes/no, area, dose), surgery (yes/no, area, type), and bone marrow transplant (yes/no) from abstracted treatment protocols.	Auditory complications (hearing loss and tinnitus) including self-reported severity and laterality (unilateral/bilateral).	Survivors reported hearing loss more frequently than siblings (p<0.001), including unilateral and bilateral, and more severe hearing loss (25%). CNS tumour survivors were at highest risk. Tinnitus prevalence was similar for survivors and siblings. Treatment with platinum compounds (cisplatin, carboplatin, or both), high doses of cranial radiation, brain surgery, or bone marrow transplant increased the risk of hearing loss among survivors. Hearing loss prevalence declined in more recent treatment periods.

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Fidler MM, 2018. (19)	British Childhood Cancer Survivor Study (BCCSS)	Population-based cohort of 5-year cancer survivors diagnosed in 1940-2006 before the age of 15 years.	34,489 survivors of all types of cancer.	Population normative data of England and Wales.	Registry-based	No treatment information assessed.	Respiratory mortality (based on ICD codes).	Survivors had a 6.8 times (95% CI: 5.8-7.9) higher risk of a respiratory death than expected in the general population, equivalent to 2.3 (95% CI: 1.8-2.7) excess respiratory deaths. Highest excess risk was observed among CNS tumour survivors. The number of excess respiratory deaths declined among survivors treated more recently (after 1990).
Reulen RC, 2017. (20)	British Childhood Cancer Survivor Study (BCCSS)	Population-based cohort of 5-year cancer survivors diagnosed in 1940-1991 before the age of 15 years.	1712 female survivors of all types of cancer with at least one recorded singleton delivery.	A random sample of 25,000 deliveries.	Registry-based	Information on site of radiotherapy treatment (none/abdominal/ cranial/other).	Pregnancy and labour complications .	All survivors treated with abdominal radiotherapy were at increased risk of gestational diabetes mellitus (RR: 3.35, 95% CI: 1.41-7.93) and anemia complicating pregnancy (RR: 2.10, 95% CI: 1.27-3.46) compared with survivors treated without radiotherapy. Survivors treated without radiotherapy had similar risks of pregnancy and labor complications as the general population.
de Vathaire F. 2012. (21)	French Childhood Cancer Survivor Study (FCCSS) + British Childhood Cancer Survivor Study (BCCSS)	Population-and institution-based cohort of 5-year survivors treated in 1995-1995 and diagnosed at age ≤16 years in France and the UK.	2520 survivors of all childhood cancers except leukaemias.	Within cohort comparison.	Questionnaire-based	Estimated radiation dose to the tail, body and head of pancreas, and radiation doses to most of the other organs of the body and 91 sites of the skeleton.	Diagnosis of diabetes mellitus (excluding gestational diabetes), self-reported and confirmed by relevant hospital doctors (France) or general practitioners (UK).	The cumulative incidence of diabetes by age 45 years was 6.6% (95% CI. 4.8-9.0%) among patients who had received radiation therapy and 2.3% (95% CI: 0.8-6.4%) among patients who had not received radiation therapy ($p<0.001$). Risk of diabetes increased strongly with radiation dose to the tail of the pancreas. No dose-response relationship was found for radiation to other parts of the pancreas. Compared with patients who did not receive radiotherapy, the relative risk of diabetes was 11.5 (95% CI 3.9–34.0) in patients who received 10 Gy or more to the tail of the pancreas.

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Mansouri I. 2018. (22)	French Childhood Cancer Survivor Study (FCCSS) - a case control study nested within the FCCSS	Institution-based cohort of 5-year survivors diagnosed before 20 years of age and treated in 1985-2000.	239 patients of all childhood cancers except leukaemias, and who have been diagnosed with heart failure.	Within cohort comparison: 1042 cardiovascular disease-free comparisons matched on gender, diagnostic age, diagnostic decade, and lenght of follow-up.	Mix of questionnaires, medical records, long-term follow-up consultation reports, and insurance and causes of death databases.	Information on chemotherapy (including drug, dose, duration, height and weight for body surface area estimation, and cumulative dose) and radiation therapy (computations of radiation dosimetry, volume metrics to estimate mean radiation doses to the heart and left ventricle).	Heart failure	The cumulative incidence of heart failure by age 30 years was 2.5% (95% CI: 2.1-2.9%) and by age 50 years it was 5.7% (95% CI: 5.0-6.6%). The risk of heart failure increased with increasing volumes of the heart and left ventricle of ≥30 Gy. The risk of heart failure also increased with cumulative dose of anthracyclines.
El-Fayech C. 2017. (23)	French Childhood Cancer Survivor Study (FCCSS)	Institution-based cohort of 5-year survivors diagnosed before 16 years of age and treated in 1985-2000.	3172 survivors of all childhood cancers.	Normative data from regional registry + within cohort comparison.	Mix of questionnaires and clinically validated.	Radiation doses to the circle of the Willis and brain structures were assessed from medical records	Stroke	Survivors receiving radiation therapy had a 8.5-fold increased risk of a stroke (95% CI: 6.3-11.0), where those not receiving radiation therapy had similar risk of stroke as the general population. For radiation dose of ≥ 40 Gy to the circle of the Willis, the risk of stroke was 15.7 (95% CI: 4.9-50.2), and risk also increased with radiation doses to the heart and neck. At 45 years of age, the cumulative stroke incidence was 11.3% (95% CI: 7.1-17.7%) in survivors who received ≥10 Gy to the circle of the Willis, compared with 1% expected from general population data.

Oudin C. 2018. (24)	French Childhood Cancer Survivor Study for Leukaemia (LEA)	Institution-based cohort of children diagnosed since 1980 with acute leukaemia below the age of 18 years, and being >18 years of age at evaluation.	1025 survivors of acute childhood leukaemia.	3203 French patients living in the area of Paris, matched on age and sex.	Clinical assessment.	Detailed history of treatment exposures were assessed from medical records with special emphasis on anthracycline cumulative dose, alkylating agents, steroids, use of radiotherapy and HSCT.	Metabolic syndrome defined according to the National Cholesterol Education Program's Adult Treatment Panel III criteria.	Survivors had metabolic syndrome more often than comparisons (10.3% vs 4.5%, OR: 2.49, 95% CI: 1.91-3.25). The cumulative incidence of metabolic syndrome at age 25 years was 7.9% (95% CI: 6.0-10.3%) and 14.4% (95% CI: 11.2-18.4%) at age 30 years. Survivors receiving HSCT had highest prevalence of metabolic syndrome, especially those who also received total body irradiation before HSCT compared with controls (OR: 6.26, 95% CI: 4.17-9.36).
Horwitz M. 2015. (25)	French Childhood Cancer Survivor Study for Leukaemia (LEA)	Institution-based cohort of children diagnosed with acute childhood leukaemia below the age of 18 years and in complete remission at time of evaluation.	271 survivors of acute childhood leukaemia who underwent HSCT.	Within cohort comparison of transplanted patients with total body irradiation-versus Busulfan-based conditionin g regimen.	Clinical assessment (slit-lamp examination) by ophthalmol ogist.	Detailed history of treatment exposures were assessed from medical records, including total body irradiation (dose and fractionation), busulfan, and cumulative steroid doses (prednisone and dexamethasone).	Cataract after HSCT.	Post-HSCT cataract occurred among 41.7% of the patients. Cataract was more frequent after allogeneic than after autologous transplantation. The 15-year cumulative incidence was 70.9% for patients receiving total body irradiation and 12.5% in the Busulfan group. Higher cumulative steroid dose was also a significant risk factor for cataract risk.
Bagnasc o F, 2019. (26)	The off-therapy registry (OTR)	Multi-institutional cohort of 5-year childhood cancer survivors who have reached completion of treatment, and have been diagnosed in 1960-1999	12,214 survivors of all childhood cancers since 1989 (stepwise inclusion of cancer types from 1960-1989).	Population normative data.	Mix of census surveys, national health registries, death certificates and/or last clinical follow-up data.	No treatment information assessed.	Overall and cause-specific mortality.	Survivors had an 11-fold increased risk of death (standardised mortality ratio (SMR): 11.0, 95% CI: 10.7-12.0), corresponding to an AER of 48 (95% CI: 45-51). The most frequent causes of death were relapse of the initial cancer (56%), subsequent primary cancers (19%), and cardiovascular events (5.8%). The probability of long-term survival at 25, 35, and 45 years from diagnosis was 91%, 87% and 81%, respectively. Mortality decreased by 60% for survivors treated most recently (1990-1999).

		before 21 years of age.						
Clemens E, 2019. (27)	PanCareLIFE Consortium**	Population- and institution-based pooled data from 14 institutions/7 countries of childhood cancer survivors off-therapy diagnosed before 20 years of age and treated in 1980-2017.	428 childhood cancer patients that were treated with cisplatin but non-cranial-irradiated, and were genotyped for 10 candidate single nucleotide polymorphisms (SNPs).	Within cohort comparison.	Clinical assessment (audiometric test).	Treatment-related data included information on platinum treatment (eg, platinum compound, dose per cycle, cumulative dose, date of start and stop treatment, and infusion duration) and potentially ototoxic co-medication (eg, amikacin, gentamycin, tobramycin, furosemide, vincristine, vancomycin) abstracted from medical records.	Platinum-induced ototoxicity/hearing loss (severity assessed using the Münster classification system, with ototoxicity defined as Münster class ≥ 2b vs no ototoxicity as Münster class 1 and 2a).	Within the cohort, 54% of patients developed minor hearing loss, and 22% of patients developed clinically relevant hearing loss after cisplatin treatment. Higher cumulative dose of cisplatin (>450 vs ≤300 mg/m2) increased the risk of ototoxicity (OR: 2.4; 95% CI: 1.3–4.6). None of the ten assessed SNPs from ten different genes were significantly associated with ototoxicity risk. A meta-analysis of this PanCareLIFE study and four previous studies indicated a significant association between the ACYP2 rs1872328 variant and cisplatin ototoxicity risk (OR: 3.94, 95% CI: 1.04–14.93), and between the SLC22A2 rs316019 and cisplatin ototoxicity risk (OR: 1.46, 95% CI: 1.07-2.00).

AER; Absolute excess risk, ALL; Acute lymphoblastic leukaemia, AML; Acute myeloid leukaemia, CML; Chronic myeloid leukaemia, CTCAE; Common Terminology Criteria for Adverse Events, CNS; Central nervous system, GSI; Global severity index, HSCT; hematopoietic stem cell transplantation, HQoL; Health-related quality of life, ICD; International classification of diseases, NCSI; National Cancer Survivorship Initiative, OR; Odds ratio, O/E; Observed/expected, RR; Risk ratio, SIR; Standardised incidence ratio, SMR; Standardised mortality ratio, SPN; Subsequent primary neoplasm

**PanCareLIFE was an EU-funded consortium active from 2013-2018, with publications expected in the years to come. http://www.pancarelife.eu/

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Table 4: Summary of the largest and most comprehensive studies on mental late effects based on childhood cancer survivor cohorts in Europe and North America, as reported by the respective cohort investigators.

Ref.	Research cohort	Setting and childhood cancer population	No. of survivors and cancer type	Comparison cohort	Outcome ascertain-ment	Cancer treatment	Outcome measures	Key findings
Brinkman TM, 2013. (28)	Childhood Cancer Survivor Study (CCSS)	Multi-institutional cohort of 5-year survivors of common childhood cancers diagnosed in 1970-1986 before the age of 21 years.	4569 survivors of leukaemia, CNS malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumour, neuroblastoma, soft tissue sarcoma and bone malignancy.	Population normative data.	Questionnaire-based	All cancer therapy was abstracted from medical records, including cumulative doses of individual chemotherapeutic agents. Radiation records were used to calculate region-specific radiation exposure.	Brief Symptom Inventory-18 to evaluate persistent depression, anxiety and somatisation.	Subsets of survivors reported persistently elevated prevalence of depression (8.9%), anxiety (4.8%), and somatisation (7.2%). Increasing distress symptoms were predicted by survivor perception of worsening physical health over time (depression OR 3.3, anxiety OR 3.0; somatisation OR 5.3).
Recklitis CJ, 2010. (29)	Childhood Cancer Survivor Study (CCSS)	Multi-institutional cohort of 5-year survivors of common childhood cancers diagnosed in 1970-1986 before the age of 21 years	9126 survivors of leukaemia, CNS malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumour, neuroblastoma, soft tissue sarcoma and bone malignancy.	2968 siblings.	Questionnaire-based	All cancer therapy was abstracted from medical records, including cumulative doses of individual chemotherapeutic agents. Radiation records were used to calculate region-specific radiation exposure.	Brief Symptom Inventory-18 to evaluate reported suicide ideation.	Among survivors, 7.8% reported suicide ideation compared with 4.6% of controls (OR: 1.79, 95% CI: 1.4-2.4). Poor physical health was significantly associated (OR 12.5, 95% CI 8.0-19.5) with suicide ideation even after adjusting for cancer diagnosis and reported depression.

Michel G, 2010. (30)	Swiss Childhood Cancer Survivor Study (SCCSS)	Population-based cohort of 5-year cancer survivors aged ≥20 years at survey and diagnosed in 1976-2003 at age ≤16 years.	987 survivors of leukaemia, lymphoma, CNS tumours, malignant solid tumour, or Langerhans cell histiocytosis.	German normative data + a population of 564 patients aged 20-49 years who received psychotherapy at the University of Bern outpatient clinic.	Questionnaire-based	Information on treatment with surgery alone, chemotherapy (without radiotherapy but may have had surgery), chemotherapy (may have had surgery and radiotherapy), bone marrow transplantation and relapse abstracted from treatment protocols.	Psychological distress assessed using the Brief Symptom Inventory instrument, and summarised in the Global Severity Index (GSI).	Survivors reported low levels of psychological distress on average, but increased distress for interpersonal sensitivity (16.5%), depression (13.4%), aggression (16.9%), and psychotic tendencies (15.6%) than the expected 10% in the norm population. Risk factors for psychological distress was female sex, being a single child, older age at study, and self-reported late effects. Comparisons with psychotherapy patients indicated that survivors' distress is clinically significant.
Deyell RJ. 2013. (31)	Childhood, adolescent, young adult cancer survivors (CAYACS)	Population-based 5-year survivors of childhood cancer diagnosed in 1970-1995 before 25 years of age.	2389 survivors of all childhood cancers.	23,890 randomly selected population comparisons from birth-cohort and gender-matched to cases.	Registry-based	Treatment data (including primary treatment modality combinations, relapse and second cancer on yes/no levels) abstracted from medical records.	Antidepressant prescriptions.	Among survivors, 21.6% filled an antidepressant prescription during follow-up compared with 18.6% among population comparisons (OR: 1.21, 95% CI: 1.09-1.35), with increased risks observed for all individual types of antidepressants and for multiple antidepressants. Survivors diagnosed between ages 15 and 20 years had nearly twice the odds of an antidepressant prescription than those diagnosed before age 5 (OR: 1.89, 95% CI: 1.04–3.45), whereas no large differences were seen for specific treatments.

AER; Absolute excess risk, ALL; Acute lymphoblastic leukaemia, AML; Acute myeloid leukaemia, CML; Chronic myeloid leukaemia, CTCAE; Common Terminology Criteria for Adverse Events, CNS; Central nervous system, GSI; Global severity index, HSCT; hematopoietic stem cell transplantation, HQoL; Health-related quality of life, ICD; International classification of diseases, NCSI; National Cancer Survivorship Initiative, OR; Odds ratio, O/E; Observed/expected, RR; Risk ratio, SIR; Standardised incidence ratio, SMR; Standardised mortality ratio, SPN; Subsequent primary neoplasm

1. Bhakta N, Liu Q, Ness KK, Baassiri M, Eissa H, Yeo F, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). The Lancet. 2017;390(10112):2569-82.
2. Mulrooney DA, Hyun G, Ness KK, Bhakta N, Pui C-H, Ehrhardt MJ, et al. The changing burden of long-term health outcomes in survivors of childhood acute lymphoblastic leukaemia: a retrospective analysis of the St Jude Lifetime Cohort Study. The Lancet Haematology. 2019;6(6):e306-e16.
3. Gibson TM, Mostoufi-Moab S, Stratton KL, Leisenring WM, Barnea D, Chow EJ, et al. Temporal patterns in the risk of chronic health conditions in survivors of childhood cancer diagnosed 1970–99: a report from the Childhood Cancer Survivor Study cohort. The Lancet Oncology. 2018;19(12):1590-601.
4. Geenen MM, Cardous-Ubbink MC, Kremer LC, Van den Bos C, Van der Pal H, Heinen RC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA. 2007;297(24):2705-15.
5. de Fine Licht S, Rugbjerg K, Gudmundsdottir T, Bonnesen TG, Asdahl PH, Holmqvist AS, et al. Long-term inpatient disease burden in the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study: A cohort study of 21,297 childhood cancer survivors. PLoS medicine. 2017;14(5):e1002296.
6. Sorensen GV, Winther JF, de Fine Licht S, Andersen KK, Holmqvist AS, Madanat-Harjuoja L, et al. Long-Term Risk of Hospitalization Among Five-Year Survivors of Childhood Leukemia in the Nordic Countries. Journal of the National Cancer Institute. 2019;111(9):943-51.
7. Lorenzi MF, Xie L, Rogers PC, Pritchard S, Goddard K, McBride ML. Hospital-related morbidity among childhood cancer survivors in British Columbia, Canada: report of the childhood, adolescent, young adult cancer survivors (CAYACS) program. International journal of cancer. 2011;128(7):1624-31.
8. McBride ML, Lorenzi MF, Page J, Broemeling A, Spinelli JJ, Goddard K, et al. Patterns of physician follow-up among young cancer survivors. Can Fam Physician. 2011;57:482-90.
9. Berbis J, Michel G, Chastagner P, Sirvent N, Demeocq F, Plantaz D, et al. A French cohort of childhood leukemia survivors: impact of hematopoietic stem cell transplantation on health status and quality of life. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2013;19(7):1065-72.
10. Teepen J, Van Leeuwen FE, Tissing WJ, Van Dulmen-den Broeder E, Van den Heuvel-Eibrink MM, Van der Pal H, et al. Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER Study Cohort: Role of chemotherapy. Journal of Clinical Oncology. 2017;35(20):2288-98.
11. Frobisher C, Glaser A, Levitt GA, Cutter DJ, Winter DL, Lancashire ER, et al. Risk stratification of childhood cancer survivors necessary for evidence-based clinical long-term follow-up. British journal of cancer. 2017;117(11):1723-31.

12. Bright CJ, Hawkins MM, Winter DL, Alessi D, Allodji RS, Bagnasco F, et al. Risk of Soft-Tissue Sarcoma Among 69 460 Five-Year Survivors of Childhood Cancer in Europe. Journal of the National Cancer Institute. 2018;110(6):649-60.
13. Allodji RS, Hawkins MM, Bright CJ, Fidler-Benaoudia MM, Winter DL, Alessi D, et al. Risk of subsequent primary leukaemias among 69,460 five-year survivors of childhood cancer diagnosed from 1940 to 2008 in Europe: A cohort study within PanCareSurFup. European journal of cancer. 2019;117:71-83.
14. Fidler MM, Reulen RC, Winter DL, Allodji RS, Bagnasco F, Bardi E, et al. Risk of Subsequent Bone Cancers Among 69 460 Five-Year Survivors of Childhood and Adolescent Cancer in Europe. Journal of the National Cancer Institute. 2018;110(2).
15. Chow EJ, Chen Y, Kremer LC, Breslow NE, Hudson MM, Armstrong GT, et al. Individual prediction of heart failure among childhood cancer survivors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(5):394-402.
16. de Fine Licht S, Winther JF, Gudmundsdottir T, Holmqvist AS, Bonnesen TG, Asdahl PH, et al. Hospital contacts for endocrine disorders in Adult Life after Childhood Cancer in Scandinavia (ALiCCS): a population-based cohort study. The Lancet. 2014;383(9933):1981-9.
17. Kasteler R, Weiss A, Schindler M, Sommer G, Latzin P, von der Weid NX, et al. Long-term pulmonary disease among Swiss childhood cancer survivors. Pediatric blood & cancer. 2018;65(1).
18. Weiss A, Sommer G, Kasteler R, Scheinemann K, Grotzer M, Kompis M, et al. Long-term auditory complications after childhood cancer: A report from the Swiss Childhood Cancer Survivor Study. Pediatric blood & cancer. 2017;64(2):364-73.
19. Fidler MM, Reulen RC, Bright CJ, Henson KE, Kelly JS, Jenney M, et al. Respiratory mortality of childhood, adolescent and young adult cancer survivors. Thorax. 2018;73:959-68.
20. Reulen RC, Bright CJ, Winter DL, Fidler MM, Wong K, Guha J, et al. Pregnancy and Labor Complications in Female Survivors of Childhood Cancer: The British Childhood Cancer Survivor Study. Journal of the National Cancer Institute. 2017;109(11).
21. de Vathaire F, El-Fayech C, Ben Ayed FF, Haddy N, Guibout C, Winter D, et al. Radiation dose to the pancreas and risk of diabetes mellitus in childhood cancer survivors: a retrospective cohort study. The Lancet Oncology. 2012;13(10):1002-10.
22. Mansouri I, Allodji RS, Hill C, El-Fayech C, Pein F, Diallo S, et al. The role of irradiated heart and left ventricular volumes in heart failure occurrence after childhood cancer. European journal of heart failure. 2019;21(4):509-18.
23. El-Fayech C, Haddy N, Allodji RS, Veres C, Diop F, Kahlouche A, et al. Cerebrovascular Diseases in Childhood Cancer Survivors: Role of the Radiation Dose to Willis Circle Arteries. International journal of radiation oncology, biology, physics. 2017;97(2):278-86.
24. Oudin C, Berbis J, Bertrand Y, Vercasson C, Thomas F, Chastagner P, et al. Prevalence and characteristics of metabolic syndrome in adults from the French childhood leukemia survivors' cohort: a comparison with controls from the French population. Haematologica. 2018;103(4):645-54.
25. Horwitz M, Auquier P, Barlogis V, Contet A, Poiree M, Kanold J, et al. Incidence and risk factors for cataract after haematopoietic stem cell transplantation for childhood leukaemia: an LEA study. British journal of haematology. 2015;168(4):518-25.

26. Bagnasco F, Caruso S, Andreano A, Valsecchi MG, Jankovic M, Biondi A, et al. Late mortality and causes of death among 5-year survivors of childhood cancer diagnosed in the period 1960-1999 and registered in the Italian Off-Therapy Registry. European journal of cancer. 2019;110:86-97.
27. Clemens E, Broer L, Langer T, Uitterlinden AG, de Vries ACH, van Grotel M, et al. Genetic variation of cisplatin-induced ototoxicity in non-cranial-irradiated pediatric patients using a candidate gene approach: The International PanCareLIFE Study. The pharmacogenomics journal. 2019.
28. Brinkman TM, Zhu L, Zeltzer LK, Recklitis CJ, Kimberg C, Zhang N, et al. Longitudinal patterns of psychological distress in adult survivors of childhood cancer. British journal of cancer. 2013;109(5):1373-81.
29. Recklitis CJ, Diller LR, Li X, Najita J, Robison LL, Zeltzer L. Suicide ideation in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(4):655-61.
30. Michel G, Rebholz CE, Von der Weid NX, Bergstraesser E, Kuehni CE. Psychological Distress in Adult Survivors of Childhood Cancer : The Swiss Childhood Cancer Survivor Study. Journal of Clinical Oncology. 2010;28(10):1740-8.
31. Deyell RJ, Lorenzi M, Ma S, Rassekh SR, Collet JP, Spinelli JJ, et al. Antidepressant use among survivors of childhood, adolescent and young adult cancer: a report of the Childhood, Adolescent and Young Adult Cancer Survivor (CAYACS) Research Program. Pediatric blood & cancer. 2013;60(5):816-22.