

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

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Keywords:

Childhood cancer; Survival; Cancer Treatment; Temporal changes; Survivorship; Somatic late effects; Mental late effects; Social and socioeconomic conditions; Survivor cohorts

Manuscript statistics

Abstract word count: 236

Manuscript word count: 3625

Authorship contributions

FE and JFW developed the concept and structure of the manuscript. All authors participated in drafting the manuscript, critically reviewed the manuscript for important intellectual content, and included revisions. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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).

Irrespective 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). Notably 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 1970-1979 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).

Acknowledgements:

We thank all the respective cohort principal investigators who have contributed with selected studies for the table (mentioned in order of appearance in the table).

On behalf of the Childhood Cancer Survivor Study (CCSS):

Dr GT Armstrong, St. Jude Children's Research Hospital, Tennessee, USA.

On behalf of the Dutch Childhood Cancer Oncology Group - Long-Term Effects After Childhood Cancer (DCOG-LATER):

Professor LCM Kremer, Princess Máxima Center for Paediatric Oncology, The Netherlands.

On behalf of the Swiss Childhood Cancer Survivor Study (SCCSS):

Professor C Kuehni, University of Bern, Switzerland.

On behalf of the British Childhood Cancer Survivor Study (BCCSS):

Professor M Hawkins, University of Birmingham, United Kingdom.

On behalf of the French Childhood Cancer Survivor Study (FCCSS):

Dr F de Vathaire, Institut Gustave Roussy, France.

On behalf of the French Childhood Cancer Survivor Study for Leukaemia (LEA Cohort):

Professor G Michel, APHM, La Timone Hospital, France and

Professor P Auquier, EA3279, School of Medicine, Aix-Marseilles University, France.

On behalf of the French Childhood Cancer Observation Platform (CCOP):

Dr J. Clavel, Inserm CRESS UMR 1153 Université de Paris, National Childhood Cancer Registry, France.

On behalf of the Off-Therapy Registry (OTR):

Dr R Haupt, Istituto Giannina Gaslini, Italy.

On behalf of the Childhood, Adolescent, and Young Adult Cancer Survivors Research Program (CAYACS):

Dr ML McBride, BC Cancer, British Columbia, Canada.

On behalf of the PanCareSurFup consortium:

Dr L Hjorth and members of the PanCareSurFup consortium.

On behalf of the PanCareLIFE consortium:

Dr P Kaatsch, Dr J Byrne and members of the PanCareLIFE consortium.

On behalf of the PanCareFollowUp consortium:

Professor LCM Kremer and members of the PanCareFollowUp consortium.

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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.

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.

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.

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%.

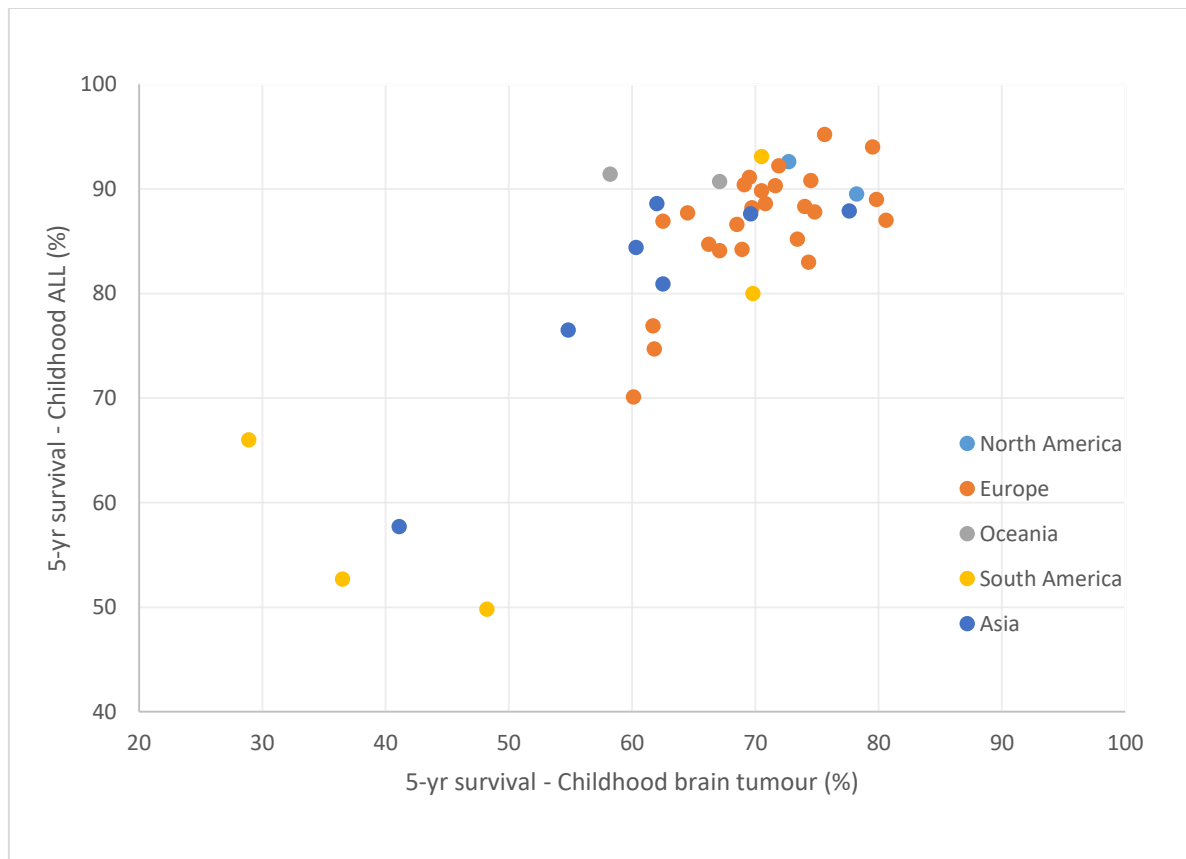


Figure 1: Distribution of worldwide 5-year age-standardised net survival estimates (%) from the CONCORD-3 study, for children diagnosed with childhood acute lymphoblastic leukaemia (ALL) and childhood brain tumours during 2010-2014. Data from CONCORD-3 (Allemani et al. 2018, Lancet) (8). Only reliable 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%.

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 ascertainment	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 musculoskeletal 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% CI: 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 at 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

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 ascertainment	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.
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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/>

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 ascertainment	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 cumulative 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-re-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-re-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.

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.

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 length 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 conditioning regimen.	Clinical assessment (slit-lamp examination) by ophthalmologist.	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.
Bagnasco 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 $\geq 2b$ 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/m ²) 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/>

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 ascertainment	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).
Recklits 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

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