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Estimating the risk for late effects of therapy in children newly diagnosed with standard risk acute lymphoblastic leukemia using an historical cohort: A report from the Childhood Cancer Survivor Study

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JH, WL, MG, CS, MMH, GTA, KRK, JPN, KCO, LLR, YY, and PCN had roles in design and conduct of the study; collection, management, analysis, and interpretation of data; and preparation, review, or approval of the Article. SE, QL, YC, and CEK had roles in analysis and interpretation of data; and preparation, review, or approval of the Article.

Conflicts of Interest

The authors declared no conflicts of interest.

Details on CCSS study design can be viewed on our website: <https://ccss.stjude.org/>

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Summary

Background—Pediatric acute lymphoblastic leukemia (ALL) therapy has evolved such that the risk for late effects in ALL survivors treated on contemporary protocols is likely different from that observed in survivors treated in prior eras. We estimated the risk for late effects in children with standard-risk ALL treated in the current era using data from similarly treated members of the Childhood Cancer Survivor Study (CCSS) cohort.

Methods—The CCSS is a multi-centre North American study of five-year survivors of childhood cancer diagnosed between 1970 and 1986. Cohort members were eligible for this analysis if they were aged 1.0–9.9 years at the time of ALL diagnosis and received therapy consistent with contemporary standard-risk ALL protocols. Outcomes were compared to a sibling cohort (n=2788) and the general United States population.

Findings—556/5980 cohort members treated for ALL met the inclusion criteria. After a median follow up of 18.4 years (range 0.0–33.0) from cohort entry, 28/556 (5%) had died (standardized mortality ratio, 3.5; 95% CI, 2.3–5.0). Sixteen deaths were due to causes other than ALL recurrence. Among 556 survivors, six (1%) developed a subsequent malignant neoplasm (standardized incidence ratio, 2.6; 95% CI, 1.0–5.7). 107 subjects in each group would need to be followed for one year in order to observe one extra chronic health condition in the ALL group compared to the sibling group (95% CI, 81–193). 415 subjects in each group would need to be followed for one year to observe one extra severe, life-threatening or fatal condition in the ALL group (95% CI, 376–939). Survivors did not differ from siblings in their educational attainment, rate of marriage or independent living.

Interpretation—Overall, the expected prevalence of adverse long-term outcomes among children treated for standard risk ALL on contemporary protocols is low, but regular care from a knowledgeable primary care practitioner is warranted.

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for more than a quarter of pediatric cancer diagnoses.¹ Improvements in therapy and supportive care have resulted in 5-year survival exceeding 80%;² in children without high-risk features, survival now exceeds 90%.³ Consequently, the population of survivors of childhood ALL living in the United States (US) exceeds 50,000.⁴

Studies of long-term survivors of ALL have demonstrated that many patients experience significant late effects of their therapy, including premature mortality, subsequent neoplasms, congestive heart failure, stroke, obesity, neurocognitive dysfunction, and osteonecrosis.^{5,6} ALL therapy has evolved substantially over time, particularly with the elimination of cranial and craniospinal radiation for the prevention of central nervous system leukemia in most patients, and the risk-adjusted use of chemotherapy to minimize the risk for late effects.⁷ Most children treated in the current era receive less intensive therapies than children treated decades ago. Consequently, the profile of late effects in newly diagnosed children is expected to differ from those observed in children treated in prior eras. This limits the ability of oncologists to extrapolate outcomes from historical cohorts in order to counsel newly diagnosed patients and their parents about future risks. Further, published surveillance guidelines for ALL survivors may not be appropriately adapted to the true risk for late effects in newly diagnosed patients.^{8,9} Although oncologists can attempt to predict late effects based on current knowledge of the long-term impacts of individual chemotherapy agents,⁷ no study has assessed the association between the totality of the treatments in contemporary ALL protocols and long-term outcomes.

In order to estimate the risk for late effects in children diagnosed with ALL today, we examined the long-term outcomes observed in members of the Childhood Cancer Survivor Study (CCSS) treated in a manner consistent with current standard-risk ALL protocols.

Methods

Characteristics of study participants

The CCSS is a longitudinal cohort study of 5-year survivors of childhood or adolescent cancer diagnosed between 1970–1986 at one of 26 institutions in North America.¹⁰ This analysis included CCSS participants who were diagnosed with ALL between the ages of 1–9 years (consistent with U.S. National Cancer Institute criteria for standard-risk ALL¹¹), completed the CCSS baseline questionnaire (<https://ccss.stjude.org/documents/original-cohort-questionnaires>), and had received ALL therapy analogous to the therapies currently used in the standard-risk ALL protocols of the Children's Oncology Group (COG)¹², St. Jude Children's Research Hospital (SJCRH)¹³, Dana-Farber Cancer Institute

(DFCI)¹⁴ and the Associazione Italiana Ematologia Oncologia Pediatrica / Berlin-Frankfurt-Münster (AIEOP/BFM)¹⁵ (table 1). Between 40–70% of current ALL patients are considered standard risk. Almost all patients with standard-risk ALL in North America, Europe, Australia/New Zealand and Japan are treated on one of these protocols or a comparable protocol. Eligible survivors had received therapy that included 0–120 mg/m² of anthracyclines and 0–1000 mg/m² of cyclophosphamide. We applied an isotoxic dose conversion (daunorubicin x 0.833) to calculate the cumulative dose of anthracyclines in doxorubicin equivalents.⁸ Between 1970 and 1986, the majority of patients with standard-risk ALL were treated with cranial irradiation; irradiated survivors were excluded from the present analysis.

CCSS has also recruited a random sample of siblings of its survivors. A control group similar in age to the ALL survivors was constructed to include siblings of survivors of any cancer type who were diagnosed between 1.0–9.9 years of age. As with the survivor cohort, siblings who had not completed the baseline questionnaire were not eligible for this analysis. Siblings completed surveys assessing the same outcomes ascertained for survivors. We used identical methods to collect information on late effects from survivors and siblings.

The Human Subjects Committee at each participating institution reviewed and approved the protocol and questionnaires. Subjects or parents (if subject was <18 years) gave consent for participation and for the release of medical records. Study materials are available at <http://ccss.stjude.org/>.

Data sources and definitions

Details regarding primary cancer and treatment received were abstracted from survivors' medical records. The National Death Index (NDI; 2007) provided information on mortality among US survivors; mortality among Canadian participants was assessed by the CCSS questionnaires. Data regarding subsequent neoplasms, chronic health conditions, health status, and socioeconomic outcomes were obtained from CCSS questionnaires. These were completed between 1992–2002 (baseline questionnaire), 2000–2002 (first follow-up), 2002–2005 (second follow-up), and 2007–2009 (third follow-up). All reported subsequent neoplasms were confirmed by study investigators and classified into subsequent malignant neoplasms (SMNs), non-malignant meningioma, and non-melanoma skin cancer according to the ICDO2 classification system. Chronic conditions were classified as time-to-event variables (SMNs, congestive heart failure, stroke and/or cerebrovascular disease, osteoporosis/osteopenia, growth hormone deficiency, cataracts, hypothyroidism) or cross-sectional variables (obesity, short stature, neurocognitive deficits). We used the data from the most recently completed questionnaire for cross-sectional variables. The severity of chronic conditions was scored based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (Version 4.03) and graded as mild (grade 1), moderate (grade 2), severe/disabling (grade 3), life-threatening (grade 4), or fatal (grade 5) as described previously.¹⁶ Obesity was defined as BMI ≥ 30 kg/m² for survivors aged ≥ 20 years at survey, or BMI > 95th percentile for survivors aged < 20 years. The Centers for Disease Control and Prevention (CDC) Year 2000 growth charts were used to define short stature among survivors < 18 years at questionnaire completion if their final height was < 2

standard deviations below the mean; survivors <18 years at last assessment were excluded from an assessment of final height.¹⁷ Neurocognitive deficits were measured by multiple items self-evaluating the frequency of specific neurocognitive symptoms in the areas of task efficiency, emotional regulation, organization, and memory.¹⁸ Responses were reported on a Likert scale that ranged from 1 (“never a problem”) to 3 (“often a problem”). Ratings were summed for each of the four factors and raw scores were converted to z-scores through reference to the sibling cohort. Z-scores ≥ 1.33 (i.e. 90th percentile of symptoms reported by the sibling cohort) were classified as impaired. The classification of impairment for scores ≥ 90 th is a standard approach when using patient reported outcomes. This threshold was used in the original development of the CCSS neurocognitive questionnaire,¹⁸ has been used in numerous subsequent publications,⁶(further reading list in appendix) and has been demonstrated to be a valid threshold comparison to direct testing using traditional neuropsychological assessment in a large cohort of adult survivors of childhood cancer.¹⁹

Health status variables - general health, mental health, functional status, activity limitations, cancer-related anxiety and cancer related pain - were assessed as published previously.²⁰ Socioeconomic outcomes included self-reported household income, education, marital status, independent living, and insurance coverage.

US mortality rates were derived from the National Center for Health Statistics (<http://www.cdc.gov/nchs/>), and reference rates for SMN (i.e., cancer incidence rates) were derived from the Surveillance, Epidemiology and End Results (SEER) Program (<http://seer.cancer.gov/>). All remaining outcomes were compared with data from questionnaires administered to the sibling controls.

Statistical analyses

Demographic characteristics of the ALL survivors and siblings, and disease and treatment characteristics of survivors, were tabulated. In order to account for the within-family correlation that results from some survivors and siblings belonging to the same family, we used bootstrapping of families, rather than individuals. This method treats each family's data as an independent random vector in a population, consistent with the construction of a standard bootstrap. We randomly selected the same numbers of families as our observed data by simple random sampling of families with replacement. In general, bootstrap is a method for constructing confidence intervals and conducting hypothesis testing on parameters of interest without making assumptions about probability distributions of data in the target population. Bootstrap methods involve taking repeated random samples of the same size from the study sample, allowing multiple inclusions of each subject, in order to draw statistical inferences about the target population. Mortality rates and standardized mortality ratios (SMRs) were calculated, stratified by sex and survival time after ALL diagnosis. SMRs were calculated by comparison to age-, sex-, and calendar year-specific US mortality rates. SMRs were also stratified by cause of death (SMN, cardiac, pulmonary, external causes, and other causes). Standardized incidence ratios (SIR) and absolute excess risk (AER) for subsequent neoplasms were calculated using age-, sex-, and calendar year-specific rates from SEER.

Cumulative incidence estimates and piecewise-exponential regression were used to analyze time-to-event outcomes. Deaths due to a non-chronic health condition, SMN, or late recurrence were treated as competing risks. Piecewise-exponential regression, adjusted for sex and age at follow-up, was used to compare survivors with siblings. Potential within-family correlation was accounted for by using the generalized estimating equation (GEE)²¹. All events contributed to the estimate of cumulative incidence. However, in the regression analyses, we excluded survivors with events within five years after their ALL diagnosis and siblings with events before the age of five. The study end time was defined as the earliest occurrence of either the outcome of interest, SMN, late ALL recurrence, last contact, or death. For SMN as the outcome of interest, we considered all SMN occurrences.

Logistic regression with GEE, adjusted for age at last questionnaire and sex, was used to compare survivors with siblings on cross-sectional outcomes. Unadjusted logistic regression was performed to compare demographic and treatment characteristics between survivors with and without a grade 3–5 condition. We also assessed the impact of high-dose methotrexate and type of corticosteroid (dexamethasone vs. prednisone) in survivors with and without cognitive late effects. Subjects with relapse/SMN prior to age 18 were excluded from analysis of final height. For the other cross-sectional outcomes, we excluded survivors who reported SMN or late recurrence before the assessment of the outcome (last questionnaire).

Number needed to harm (NNH) was calculated by subtracting the risk measures (rate for time-to-event outcomes; prevalence for cross-sectional outcomes) in siblings from those in survivors, and calculating the inverse of the difference. NNH, adjusted for gender and age at response to the questionnaire, indicates the number of person-years of ALL survivor follow-up that would result in the observation of one extra survivor developing a chronic health condition compared to the sibling group (time-to-event outcomes), or the number of ALL survivors that need to be followed in order to observe one extra survivor developing a chronic condition compared to the sibling group (cross-sectional outcomes). A negative number indicates higher risk in the sibling group compared to the ALL group. The 95% confidence intervals of NNH were estimated using bootstrapping of families. One thousand bootstraps were used to derive the estimates.

Analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC, USA). Our manuscript is presented in a manner consistent with the STROBE statement (appendix).

RESULTS

Characteristics of the Study Population

Of 5980 ALL survivors in the CCSS, 556 met the inclusion criteria for this analysis (Figure 1). Of 4023 siblings, 2232 met the inclusion criteria for the control group. The demographic, disease and treatment characteristics of the survivors and siblings are displayed in table 2. The median follow-up of the ALL survivors from 5 years after diagnosis was 18.4 years (interquartile range 16.0 to 21.5, range 0.0 to 33.0) and the median age at completion of the most recent study questionnaire was 27.8 (range 9.1 to 45.7). Survivors were younger than siblings at most recent questionnaire ($p < 0.0001$). Among those included, 460 (83%) of 556

survivors and 1373 (62%) of 2232 siblings completed the first follow-up questionnaire; 418 (75%) and 1617 (72%), respectively, completed the second follow-up questionnaire; and 374 (67%) and 1258 (56%), respectively, completed the third follow-up questionnaire. 331 (60%) survivors and 855 (38%) siblings completed the baseline and all three follow-up questionnaires.

Mortality

Twenty-eight of the 556 5-year ALL survivors died at a median of 14.4 years (range 5.0–36.6 years) from diagnosis (SMR 3.5; 95% CI 2.3 to 5.0) (table 3). SMR was highest in years 5–9 after diagnosis and decreased over time (p -for-trend=0.0008). Twelve deaths were due to late ALL recurrence (>5 years from diagnosis). Of the remaining 16 deaths, two were due to a SMN, one was due to cardiac disease, eight were a result of external causes (four motor vehicle accidents, two other accidents, one suicide, and one poisoning), and six due to other or unknown causes. Overall, survivors were at increased risk for non-relapse mortality (SMR 2.0; 1.1 to 3.2), but there was no significant difference compared to the general population in risk for death due to a new malignancy, cardiac disease, pulmonary disease or external causes (homicide, suicide, accident).

Subsequent neoplasms

We observed six SMNs, one non-malignant meningioma and no cases of non-melanoma skin cancer. The SIR for SMN was 2.6 (95% CI, 1.0 to 5.7), and the AER was 0.4 (0.0 to 1.1). The six SMNs consisted of two melanomas, one astrocytoma, one large cell lymphoma, one leukemia, and one hepatocellular carcinoma.

Chronic physical health conditions

Figure 2 (appendix) demonstrates the cumulative incidence of chronic conditions among survivors and siblings. By the age of 35, a chronic health condition was reported by 70% of survivors and 62% of siblings; 48% of survivors and 33% of siblings reported multiple chronic health conditions, and 16% and 9%, respectively, reported a severe or life-threatening (CTCAE grade 3–4) condition. The most frequent chronic condition observed among survivors and siblings was migraine (30% and 25%, respectively). The next-most frequent conditions reported by survivors and siblings were emphysema (14% and 14%, respectively), hypertension (13% and 9%), and sensory neuropathy (13% and 9%). Survivors were at a slight increased risk for reporting a chronic medical condition when adjusted for age at follow-up and sex (rate ratio 1.3; 95% CI 1.1 to 1.6; table 4). This corresponds to following 107 subjects per group for one year (or eleven subjects for ten years) in order to observe one extra subject in the ALL survivor group compared to the sibling control group with one or more chronic health conditions (95% CI, 81 to 193). Survivors were at increased risk for reporting a severe or life-threatening condition (rate ratio 2.0, 95% CI 1.4 to 2.8; 415 subjects per group followed for one year to observe one extra survivor with a condition, 95% CI 376 to 939), or multiple conditions (rate ratio 1.6; 95% CI 1.4 to 2.0; 136 subjects per group followed for one year to observe one extra survivor with multiple conditions, 95% CI 126 to 236). Compared to siblings, survivors were at increased risk for developing osteoporosis or osteopenia, growth hormone deficiency, cataracts, and short stature. There was no statistically significant increase in risk

for congestive heart failure or cardiomyopathy, stroke or cerebrovascular disease, or hypothyroidism. No survivors required medication or heart transplantation due to heart failure or cardiomyopathy. Risk factors for developing a grade 3 to 5 chronic health condition are presented in table 5. Only those survivors treated in earlier years and those older at most recent questionnaire were at increased risk. High-dose methotrexate and type of corticosteroid used were not associated with cognitive late effects.

Health status and sociodemographic outcomes

Survivors reported poor functional status twice as frequently as siblings (39 of 506 [8%] survivors vs. 69 of 1763 [4%] siblings, odds ratio 1.9; 95% CI 1.3 to 2.9; need to follow up 27 ALL survivors and 27 siblings in order to observe one extra survivor with poor functional status, 95% CI 16 to 104). However, there was no difference in their reporting of fair or poor general health, poor mental health, or activity limitations. Similarly, survivors did not differ from siblings in terms of household income, educational attainment, marital status, likelihood of living independently, or rates of insurance coverage (table 6).

Discussion

This study assessed the health, health status and socioeconomic outcomes of 556 long-term survivors of childhood ALL who were treated in a manner analogous to contemporary standard-risk ALL therapy. At an average of 23.4 years from their ALL diagnosis, this cohort appeared to be at only moderately increased risk for some chronic health conditions or decreased health status, and had socioeconomic outcomes comparable to a group of siblings who did not develop cancer as children.

Even among survivors who were five or more years from their ALL diagnosis, the most frequent cause of premature death was ALL recurrence. This finding is consistent with published data that has described relapse rates after 5 and 10 years of follow-up of 3% and 1% respectively, and a high proportion of subsequent deaths due to relapse.^{22,23} Overall, survivors were at slightly increased risk for late death due to non-relapse causes; however, no individual cause of premature death was increased when compared to the general population. The elimination of radiation from standard risk ALL protocols and the restricted use of chemotherapy agents linked to increased risk for SMN (e.g. alkylating agents) and cardiac disease (e.g. anthracyclines) likely contribute to the low risk for premature death observed in the cohort.

Although the risk for most chronic health conditions did not differ from that observed in siblings, there were a small number of conditions that were more prevalent in survivors. In particular, we found an increased risk for osteoporosis or osteopenia, growth hormone deficiency and short stature, and cataracts. Prior studies have demonstrated a dose-dependent decrease in bone mineral density after exposure to methotrexate and corticosteroids,²⁴ and cataracts have been attributed to the use of corticosteroids.²⁵ While the predominant contributor to short stature in survivors of childhood ALL is cranial irradiation, chemotherapy alone has been shown to be associated with a small increase in risk.²⁶ However, our observation of an increased risk for growth hormone deficiency was unexpected since this outcome is generally attributed to the use of cranial or craniospinal

irradiation.²⁷ In other chronic childhood diseases, prolonged corticosteroid use is known to cause short stature by affecting growth hormone secretion, inhibiting IGF production, and interfering with bone metabolism.²⁸

Most survivors reported health status and socioeconomic outcomes comparable to siblings. Survivors were as likely as siblings to report good general and mental health, and to marry, live independently, graduate college/university and to be insured. However, twice as many survivors (15%) reported poor functional status compared with siblings. A Dutch cohort of survivors of assorted malignancies found similar results: childhood cancer survivors were at increased risk for decrements in physical and social functioning, and role limitations due to physical problems compared to age and sex matched peers.²⁹ However, cohorts of non-irradiated Finnish and Swiss ALL survivors were not at increased risk for impaired functional status.^{30,31} A French cohort study also demonstrated no difference in physical quality of life.³² Poor functional status has typically been associated with amputations and neurological late effects in survivors of bone or CNS tumours, or ALL treated with cranial radiation.²⁰ Therefore, our findings were unexpected, particularly because childhood cancer survivors often rate their health as better than population controls because they tend to minimize difficulties, or experience post-traumatic growth.^{33,34}

The findings of this study should be interpreted in the context of a few limitations. The ranges of chemotherapy dosing considered to be analogous to contemporary protocols were derived from expert consensus. Only anthracycline and alkylating doses were considered to be important determinants of dose-dependent long-term risks. A minority of participants received an anthracycline. This limits our ability to infer conclusions about the impact of lower doses of anthracyclines on the risk for cardiac late effects. Data from ALL populations at Dana-Farber Cancer Institute and Emma Children's Hospital/Academic Medical Center suggest a low risk for clinical cardiac disease in survivors who received less than 300mg/m² of anthracyclines.³⁵ This is comparable to our observations; however our questionnaires were not designed to detect sub-clinical cardiac dysfunction that has not resulted in medical intervention.¹⁷ Although most of the other chemotherapy agents used in ALL protocols are not considered to cause long-term harm, there is some evidence that high-dose methotrexate and the type of corticosteroid used (dexamethasone vs. prednisone) may be associated with differential risk for neurocognitive dysfunction.³⁶ Conversely, other studies have not demonstrated a difference in neurocognitive outcomes between those treated with dexamethasone versus prednisone.³⁷ We did not observe differences in neurocognitive outcomes in children treated with or without high-dose methotrexate or those that received dexamethasone compared to prednisone. There is evidence to suggest that self-report of neurocognitive symptoms may underestimate true functional deficits,³⁸ and thus might not be sensitive to potentially mild cognitive deficits. Another late effect linked to corticosteroid use is osteonecrosis (avascular necrosis). However, an increased risk for osteonecrosis in children treated with dexamethasone versus prednisone has only been observed in teenagers, and has not been shown to be an issue in the children <10 years of age³⁹ who are the focus of the present study. The size of the cohort may have limited our ability to detect rare outcomes; however, to our knowledge, this is the largest cohort of ALL survivors treated as per contemporary protocols that has been assessed for very long-term outcomes. Another possible limitation is the use of siblings as a control group since they might be impacted by

the cancer experience. Most siblings have favorable physical, psychological and psychosocial outcomes, but some have been shown to be at risk for inferior health status and socioeconomic outcomes compared to the general population.⁴⁰ This might lead to an underestimation of the relative risk in survivors. At the same time, missing ascertainment for outcomes in siblings that only become obvious with specific measurements (e.g. bone mineral density during follow-up care) might lead to an overestimation of the relative risk in survivors. Since most chronic disease outcomes (other than SMN and death) have not been independently validated, readers must consider this limitation when interpreting risk in both siblings and controls. Among a randomly selected sample of survivors, their nearest aged sibling was invited to participate in the sibling cohort. Non-participating siblings did not provide any descriptive information and thus there is no way of knowing whether the participating siblings are different from the non-participating siblings. Inclusion of siblings of children with any cancer diagnosis (not just ALL) allowed for the inclusion of a larger control group, increasing the precision of the comparisons between survivors and controls. Although we included children with ALL who received therapies comparable to contemporary protocols, methods of chemotherapy administration and supportive care have evolved over time and may modify the outcomes in newly diagnosed patients. Although this might lead to an overestimation of the risks in today's survivors, these differences are likely to be minor.

The long-term outcomes in the present cohort of ALL survivors, now an average of 23 years from diagnosis, will inform the counselling of patients treated for standard risk ALL on contemporary protocols. Our findings suggest that their major long-term risks are for death due to late relapse, and the development of osteoporosis, cataracts, and poor functional status. However, the prevalence of adverse long-term outcomes is low, and most survivors of ALL treated on contemporary protocols can be anticipated to have physical, psychosocial and socioeconomic outcomes comparable to the general population. Several large cohort studies are following childhood cancer survivors longitudinally.^{10,41} As survivors in these cohorts age, detection of an increased risk for clinically relevant very late outcomes might prompt a revision of the outlook and follow-up guidelines. The optimal model of care for ALL survivors remains to be defined, but it appears that survivors of standard-risk ALL can be adequately cared for by a primary care practitioner who has been provided an appropriate treatment summary and recommendations for surveillance and health maintenance.⁴² Further research is needed to compare the health benefits of long-term surveillance in low-risk survivors with the psychosocial impact of ongoing surveillance. Our findings suggest that oncologists meeting with newly diagnosed patients with standard risk ALL can reassure patients and their families that both the prognosis for disease survival and their prospects for long-term health are good.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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The funding sources had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (PCN) had full access to all data, and had final responsibility to submit the report for publication.

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Panel: Research in context**Systematic review**

We searched PubMed with the terms “acute lymphoblastic leukemia”, “childhood”, “survivors”, and “late effects” for studies published before Jan 1, 2014. We identified long-term follow-up studies of childhood leukemia survivors in the US and Canada,^{5,6,18,20,26} the UK,⁴³ the Netherlands,³⁵ Switzerland,³¹ Finland,³⁰ and France²⁵. The studies were broad in study design (questionnaire and cohort studies, registry data etc.), participant selection (nationwide samples, visitors of follow-up clinics etc.) and outcomes (mortality, morbidity, quality of life).

Interpretation

To our knowledge, this study is the first to focus on anticipated late-effects among very long-term survivors of ALL treated according to contemporary therapies. Since more than 90% of children treated for standard risk ALL will become long-term survivors, and ALL is the most common childhood malignancy, this subset of patients will comprise a significant proportion of the growing survivor population. Our results allow oncologists to reassure newly diagnosed patients with standard risk ALL and their families that their prognosis for long-term disease-free survival and their prospects for long-term health are good.

Figure 1.
Diagram of ALL survivors in the Childhood Cancer Survivors Study

Table 1

Cumulative doses of chemotherapy and radiation in current standard-risk ALL therapy protocols and definition of dose ranges for inclusion for CCSS sub-cohort of ALL survivors in analysis

	Contemporary ALL therapy protocols					Eligible dose range	
	COG-AALL0932 average risk arm A		SJCRH Total Therapy XV study Low risk		DFCI protocol (2012)	AIEOP-BFM ALL 2009	CCSS
	female	male	female	male			
Dexamethasone (mg/m ²)	908	1298	1160	1160	1020	210 (+tapering)	any
Prednisone (mg/m ²)	0	0	1120	1120	1280	1680 (+tapering)	any
Asparaginase (IU/m ²)	5000 (PEG i.v.)	5000 (PEG i.v.)	240000 (E.coli i.m.)	240000 (E.coli i.m.)	40000 (PEG i.v.) or 2500 (PEG i.v.) then 750000 (E.coli i.m.)	7500 (PEG i.v.)	any
Doxorubicin (mg/m ²)	75	75	60	60	60	120	Cumulative
Daunorubicin (mg/m ²)	0	0	50	50	0	0	anthracycline dose 0 – 120
Cyclophosphamide (mg/m ²)	1000	1000	1000	1000	0	120	0 – 1000
Cytarabine (mg/m ²)	600	600	600	600	0	1800	any
Methotrexate HD (mg/m ²)	0	0	11000	11000	5000	20000	any
Methotrexate i.v. (mg/m ²)	2000	2000	3640 (i.v./i.m.)	4680 (i.v./i.m.)	2970 (i.v./i.m.)	0	any
Methotrexate p.o. (mg/m ²)	1480	2420	0	0	0	0	any
Mercaptopurine (mg/m ²)	42000	69300	63490	77140	24500	3080 + ca. 25900	any
Thioguanine (mg/m ²)	840	840	0	0	0	840	any
Vincristine (mg/m ²)	57	76.5	61	61	76	12	any
Intrathecal chemotherapy (#doses)	17	22	13 (17 for CNS high risk) triple IT after first	13 (17 for CNS high risk) triple IT after first	16	9 (11 for CNS2/TLP+, 13 for CNS pos)	any
Radiation (Gy)	0	0	0	0	0	0 (18 Gy for CNS+)	0

ALL=acute lymphoblastic leukemia. CCSS=Childhood Cancer Survivor Study. COG=Children's Oncology Group. SJCRH=St. Jude Children's Research Hospital. DFCI=Dana-Farber Cancer Institute. AIEOP-BFM=Associazione Italiana Ematologia Oncologia Pediatrica-Berlin-Frankfurt-Munster.

PEG=polyethylene glycol. HD=high dose. i.v.=intravenous. p.o.=per os. CNS=central nervous system. IT=intrathecal. CNS2/TLP+=central nervous system status 5 white blood cells per microliter cerebrospinal fluid with blasts/traumatic lumbar puncture positive.

Table 2

Characteristics of study population

	Survivors n=556 n (%)	Siblings n=2232* n (%)	p value‡
Gender			.10
Female	302 (54)	1105 (50)	
Male	254 (46)	1127 (51)	
Age at most recent questionnaire (years)			<.0001
<20	65 (12)	199 (9)	
20 to 29	308 (55)	921 (41)	
30 to 39	158 (28)	842 (38)	
40 to 60	25 (5)	270 (12)	
Race/ethnicity‡			.45‡
White	497 (89)	1893 (88)	
Black	13 (2)	76 (4)	
Hispanic	28 (5)	94 (4)	
Other	18 (3)	78 (4)	
Year of diagnosis			
1970 to 1974	57 (10)		
1975 to 1979	57 (10)		
1980 to 1986	442 (80)		
Age at diagnosis (years)			
0 to 4	385 (69)		
5 to 9	171 (31)		
Received anthracyclines			
Yes	33 (6)		
No	523 (94)		
Alkylating agent score			
0	468 (88)		
1	65 (12)		
Cumulative dose of Methotrexate (mg/m²)§			

	Survivors n=556 n (%)	Siblings n=2232* n (%)	p value‡
<1000	355 (68)		
1000	171 (33)		
Type of Steroids			
Prednisone only	503 (91)		
Prednisone & Dexamethasone	43 (8)		

* The sibling group includes all siblings of CCSS survivors who were diagnosed at age 1 to 10 regardless of diagnosis.

† Race/ethnicity was missing for 91 (4.0%) siblings. They were deleted casewise in the regression modelling.

‡ The p-value considered the correlation between family members.

§ all administration routes combined

Table 3

Late mortality in survivors

	n	Rate*	SMR (95% CI)
All deaths	28	2.5	3.5 (2.3 to 5.0)
Gender			
Female	11	1.8	4.2 (2.1 to 7.5)
Male	17	3.4	3.1 (1.8 to 5.0)
Time after diagnosis (years)			
5 to 9	7	2.5	8.1 (3.2 to 16.7)
10 to 14	10	3.7	5.6 (2.7 to 10.3)
15 to 19	7	2.6	3.0 (1.2 to 6.2)
20 and over	4	1.4	1.3 (0.4 to 3.3)

SMR=standardized mortality ratio.

* Deaths per 1,000 person-years.

Table 4

Chronic health conditions in survivors and siblings

	Survivors n=556 n (%)	Siblings n=2232 n (%)	Rate Ratio/Odds ratio (95% CI) *	p value	Number needed to harm (95% CI) //
Overall chronic health conditions					
Any condition grade 1–5	192 (48)	1058 (51)	1.3 (1.1 to 1.6)	.0005	107 (81 to 193)
Any condition grade 3–5	51 (10)	157 (7)	2.0 (1.4 to 2.8)	<.0001	415 (376 to 939)
Multiple conditions 1–5	156 (32)	598 (27)	1.6 (1.4 to 2.0)	<.0001	136 (126 to 236)
Multiple conditions 3–5	6 (1)	18 (1)	1.8 (0.7 to 4.8)	.21	-
Specific health conditions					
Second malignant neoplasm	6 (1)	15 (1)	2.2 (0.8 to 6.2)	.13	-
Congestive heart failure or cardiomyopathy	1 (1)	4 (1)	1.5 (0.2 to 11.8)	.68	-
Stroke and/or cerebrovascular disease	2 (1)	4 (1)	3.3 (0.5 to 22.8)	.23	-
Osteoporosis or osteopenia	6 (1)	10 (1)	5.5 (1.5 to 19.5)	.0089	4084 (2581 to >9999)
Growth hormone deficiency	7 (1)	4 (1)	13.9 (2.8 to 68.1)	.0012	-
Cataracts	7 (1)	10 (1)	5.0 (1.7 to 14.5)	.0032	1816 (1387 to >9999)
Hypothyroidism grade 1–2	12 (2)	50 (2)	1.4 (0.7 to 2.4)	.36	17370 (< -9999 to >9999)
Obesity at last contact					
No (ref) †	397 (79)	1722 (79)			
Yes	103 (21)	448 (21)	1.1 (0.9 to 1.4) ‡	.40	60 (-335 to 476)
Final height					
Normal (ref)	441 (97)	2015 (99)			
Short stature	16 (4)	19 (1)	3.9 (2.0 to 7.7) ‡§	<.0001	39 (21 to 95)
Neurocognitive deficits					
No (ref)	208 (67)	147 (72)			
Yes	105 (34)	56 (28)	1.2 (0.8 to 1.8) ‡	.48	-

NNH=Number needed to harm.

* Rate Ratios adjusted for gender, and age at follow-up. Odds ratios adjusted for gender and age at response to questionnaire.

† Proportions of survivors and siblings overweight, normal weight and underweight are presented in the webappendix.

‡ Obesity, final height and neurocognitive deficits are cross-sectional outcomes and therefore presented as prevalent cases and odds ratios.

[§] Odds Ratios for short status was not adjusted for age at response to questionnaire. Subjects who were less than 18 years old at last assessment and those who had a relapse or second malignant neoplasm before 18 years old were excluded from the analysis of short status.

// NNH adjusted for gender and age at response to questionnaire; it was not possible to calculate NNH for all outcomes due to small numbers.

Table 5

Comparison of survivors with and without grade 3–5 chronic health conditions

	Survivors with any grade 3–5 condition n=51	Survivors without no grade 3–5 condition n=485	Odds Ratio/Mean difference (95% CI)	p value
Gender				
Female (ref)	28 (55)	263 (54)		
Male	23 (45)	222 (46)	1.1 (0.5 to 1.7)	.93
Mean age at most recent questionnaire (years)	30.0 (6.6)	27.5 (6.4)	2.5 (–4.3 to 0.6)	.0094
Race/ethnicity				.69
White (ref)	46 (90)	433 (89)		
Black	2 (4)	11 (2)	1.7 (0.4 to 8.0)	.36
Hispanic	1 (2)	25 (5)	0.4 (0.1 to 2.8)	.26
Other	2 (4)	16 (3)	1.2 (0.3 to 5.3)	.72
Year of diagnosis				.018
1970 to 1974 (ref)	10 (20)	43 (9)		
1975 to 1979	8 (16)	48 (10)	0.7 (0.3 to 2.0)	.68
1980 to 1986	33 (65)	394 (81)	0.4 (0.2 to 0.8)	.0069
Mean age at diagnosis (years)	4.4 (1.9)	4.6 (2.1)	–0.2 (–0.7 to 0.4)	.93
Steroids				.84
None (ref)	1 (2)	6 (1)		
Prednisone only	45 (88)	439 (91)	0.6 (0.1 to 5.2)	.57
Prednisone and Dexamethasone	5 (10)	40 (8)	0.8 (0.1 to 7.6)	.95
Methotrexate, mg/m ² *				
<1000	32 (65)	314 (68)		
1000	17 (35)	149 (32)	1.1 (0.6 to 2.1)	.72
Overall alkylating agent score [†]				
0 (ref)	41 (85)	409 (88)		
1	7 (15)	57 (12)	1.2 (0.5 to 2.9)	.64
Anthracyclines				
No (ref)	51 (100)	454 (94)		
Yes	0.0 (0)	31 (6)	-	-

Data are number (%) and odds ratio for categorical outcomes, or mean (SD) and mean difference (95% CI) for continuous outcomes.

* All administration routes combined.

[†] Based on number of alkylating agents and cumulative dose.

Table 6
Comparison of health status and sociodemographic outcomes between survivors and siblings

	Survivors n=556 n (%)	Siblings n=2232 n (%)	Odds Ratio (95% CI) [*]	p value	Number needed to harm (95% CI) [†]
Health status					
General health					
Excellent/Very good/Good (ref)	475 (94)	1696 (95)			
Fair/Poor ¹	29 (6)	97 (5)	1.1 (0.7 to 1.7)	.64	177 (-2331 to 2045)
Mental health					
Good (ref)	374 (88)	1836 (91)			
Poor ²	52 (12)	183 (9)	1.3 (0.9 to 1.8)	.14	43 (-391 to 427)
Functional status					
Good (ref)	467 (92)	1694 (96)			
Poor ³	39 (8)	69 (4)	1.9 (1.3 to 2.9)	.0017	27 (16 to 104)
Activity limitations					
No (ref)	434 (85)	1555 (88)			
Yes ⁴	78 (15)	220 (12)	1.4 (1.0 to 1.8)	.041	29 (21 to 171)
Cancer-related Pain					
No (ref)	379 (89)	-	-	-	
Yes ⁵	47 (11)	-	-	-	
Cancer-related anxiety/fear					
No (ref)	444 (90)	-	-	-	
Yes ⁶	48 (10)	-	-	-	
Sociodemographic outcomes					
Household income					
\$60,000(ref)	209 (45)	994 (51)			
< \$60,000	254 (55)	972 (49)	1.0 (0.8 to 1.2)	.97	-220 (-538 to 664)
Education					
College graduate (ref)	210 (45)	922 (45)			
Less than college graduate	254 (55)	1108 (55)	0.8 (0.7 to 1.0)	.076	-
Marital status					

	Survivors n=556 n (%)	Siblings n=2232 n (%)	Odds Ratio (95% CI) [*]	p value	Number needed to harm (95% CI) [†]
Married/living with a partner/Widowed/divorced/separated (ref)	240 (58)	1138 (67)			
Single	172 (42)	554 (33)	1.1 (0.9 to 1.4)	.43	-
Living independently					
Yes (ref)	314 (78)	1405 (83)			
No ⁷	87 (22)	291 (17)	1.2 (0.6 to 1.6)	.43	43 (-388 to 323)
Insurance coverage					
uninsured (ref)	70 (14)	278 (13)			
Public/Private health insurance	434 (86)	1921 (87)	1.0 (0.7 to 1.3)	.86	-348 (-1086 to 901)

Subjects with a second malignant neoplasm or recurrence before last questionnaire or with missing data were removed before analysis; n (%) in the table presents the number of events and the percentage in the cohort after removal of these subjects.

* Odds Ratios adjusted for gender, and age at response to questionnaire.

[†] NNH adjusted for gender and age at response to questionnaire (except final height); it was not possible to calculate NNH for all outcomes due to small numbers.

1 "fair" or "poor" in SF-36 question "Would you say that your health is excellent, very good, good, fair, or poor?"

2 T-scores 63 in any of BSI-18's symptom specific subscales: depression, somatization or anxiety

3 "yes" to any of these 3 questions: if they had any impairment or health problem that resulted in (1) needing "help with personal care needs, such as eating, bathing, dressing, or getting around your home"; (2) needing "help in handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes"; or (3) "keeping you from holding a job or attending school."

4 "yes" to any of these 3 questions: if in the last 2 years their health was limited for more than 3 months in (1) the kinds or amounts of moderate activities you can do, like moving a table, carrying groceries, or bowling; (2) walking upstairs or climbing a few flights of stairs; or (3) walking one block), cancer-related pain (yes if "moderate", "severe" or "very severe" in "Do you currently have pain as a result of your cancer or its treatment?"

5 "moderate", "severe" or "very severe" in response to the question: "Do you currently have pain as a result of your cancer or its treatment?"

6 "medium", "a lot of" or "very many, extreme anxiety/fears" in response to the question: "Do you currently have anxiety/fears as a result of your cancer or its treatment?"

7 "live with parent," "live with brothers and/or sisters," "live with other relatives," or specified that they had nursing or caregiver support under "other" living arrangements