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Temporal patterns in the risk of chronic health conditions among survivors of childhood cancer diagnosed 1970-1999: a report from the Childhood Cancer Survivor Study cohort

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Abstract

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Author Contributions

GTA, MMH and LLR provided financial support. EJC, SSD, RMH, MMH, PCN, CAS, GTA, LLR and KCO provided study materials and patients. TMG, SM-M, KLS, WML, DB, EJC, MMH, PCN, CAS, EST, EMW, GTA, LLR, and KCO obtained and assembled data. TMG, SM-M, KLS, and WML analysed the data. TMG, SM-M, KLS, WML, GTA, LLR, and KCO were responsible for the preparation and writing of the manuscript. All authors conceived and designed the study, interpreted the data, contributed to the manuscript, and approved the final version of the manuscript.

Declaration of interests

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Background: Treatments for childhood cancer have evolved in recent decades, with the goal of maximizing cure rates while minimizing the adverse effects of therapy. We aimed to evaluate incidence patterns of serious chronic health conditions in long-term survivors of childhood cancer across three decades of diagnosis and treatment.

Methods: We used data from the Childhood Cancer Survivor Study, a retrospective cohort with prospective follow-up of 5-year survivors of childhood cancer diagnosed from 1970-1999 in North America. We examined the cumulative incidence of severe to fatal chronic health conditions occurring up to 20 years post-diagnosis among survivors, compared by diagnosis decade. Multivariable regression models estimated hazard ratios per diagnosis decade, and addition of treatment variables assessed whether treatment changes attenuated associations between diagnosis decade and chronic disease risk.

Findings: Among 23,601 survivors (median age 28, range 5-63 years; 46% female), the 20-year cumulative incidence of at least one grade 3-5 chronic condition decreased significantly from 33·2% (95% CI, 32·0%-34·3%) in those diagnosed 1970-1979 to 29·3% (95% CI, 28·4%-30·2%, p<0·0001) in 1980-1989, and 27·5% (95% CI, 26·4%-28·6%, p=0·012 vs. 1980-1989) in 1990-1999. By comparison, the 20-year cumulative incidence of at least one grade 3-5 condition among 5,051 siblings was 4·6% (95% CI,3·9%-5·2%). The 15-year cumulative incidence of at least one grade 3-5 condition was lower for survivors diagnosed 1990-1999 compared to 1970-1979 for Hodgkin lymphoma (17·7% vs. 26·4%, p<0·0001), non-Hodgkin lymphoma (16·9% vs. 23·8%, p=0.0053), astrocytoma (30·5% vs. 47·3%, p<0·0001), Wilms tumor (11·9% vs. 17·6%, p=0·034), soft tissue sarcoma (28·3% vs. 36·5%, p=0·021), and osteosarcoma (65·6% vs. 87·5%, p<0·0001). In contrast, the 15-year cumulative incidence of at least one grade 3-5 condition was higher (1990-1999 vs. 1970-1979) for medulloblastoma/PNET (58·9% vs. 42·9%, p=0·00060) and neuroblastoma (25·0% vs. 18·0%, p=0·0045). Results were consistent with changes in treatment as a mediator of the association between diagnosis decade and risk of grade 3-5 chronic conditions for astrocytoma, Hodgkin lymphoma, and non-Hodgkin lymphoma. Temporal decreases were observed for endocrinopathies, subsequent malignant neoplasms, musculoskeletal conditions, and gastrointestinal conditions, while hearing loss increased.

Interpretation: Our results provide novel evidence that more recently treated survivors of childhood cancer have experienced improvements in health outcomes, consistent with efforts over the same time period to modify childhood cancer treatment regimens to maximize cure while reducing risk of late effects. Continuing advances in cancer therapy offer promise of further reducing the risk of late effects. However, achieving a cure for childhood cancer continues to come at a cost for many survivors, emphasizing the importance of long-term follow-up care for this population.

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INTRODUCTION

There are more than 420,000 survivors of childhood cancer in the U.S. and this number is estimated to exceed half a million by 2020.[1] More than 80% of children diagnosed with a malignancy now achieve 5-year survival, but these individuals have substantial risk of morbidity and mortality later in life due to the late effects of cancer and its treatments.[1–4] A previous study in the Childhood Cancer Survivor Study (CCSS) reported that 53·6% of long-

term childhood cancer survivors, diagnosed 1970-1986, developed at least one severe, disabling, life-threatening, or fatal chronic health condition by age 50, representing a five-fold increased risk compared to siblings.[5] In a single institution study, Hudson et al reported that 80·5% of survivors who underwent systematic clinical assessment were identified with at least one severe, disabling, or life-threatening chronic health condition by age 45.[6]

Associations between specific cancer therapies and increased risk of late effects in survivors have led to modifications in treatment regimens with the goal of maintaining or improving cure rates while reducing the risk and severity of late effects. For some cancers, elimination of radiation or combinations of conformal fields and dose reductions were able to minimize exposure to healthy tissues while maintaining therapeutic efficacy.[7–10] Furthermore, risk-adapted therapy has allowed reduced treatment exposures for children with a lower risk of relapse or recurrence of their primary cancer.[7,8] These changes contributed to reduced late mortality from late effects among survivors treated in more recent decades.[11–13] In contrast, survivors treated more recently have reported reduced, not improved, health status, emphasizing the need to further examine temporal changes in chronic health conditions in this population.[14] Optimum survivorship should include both extended lifespan and improvements in overall health; therefore, the goal of our analysis was to examine associations between treatment era and the incidence of severe, disabling, life-threatening, or fatal chronic health conditions, utilizing the expanded CCSS cohort of five-year survivors diagnosed from 1970-1999.

METHODS

Study design and participants

The CCSS is a multi-institutional retrospective cohort study with longitudinal follow-up of survivors of common childhood cancers (leukemia, tumors of the central nervous system, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, or bone tumors) diagnosed prior to age 21 at one of 27 institutions in the U.S. and Canada. Survivors were eligible if they were diagnosed with cancer between January 1, 1970 and December 31, 1999 and survived at least five years. For this analysis, we included all participants who completed the baseline questionnaire. Survivors diagnosed 1970-1986 completed the baseline questionnaire primarily from 1994-1998 (range 1992-2004), and survivors diagnosed 1987-1999 completed the baseline questionnaire primarily from 2008-2013 (range 2007-2014). Closest age siblings of a random sample of survivors were recruited to serve as a comparison group. The design and methods of the study have been described previously.[15,16] The institutional review boards of the participating institutions approved the CCSS protocol, and participants provided informed consent.

Procedures

Detailed information on cancer treatments received within five years of initial diagnosis was abstracted from medical records, including chemotherapy cumulative doses and body region-specific radiation dosimetry.[17] Anthracycline doses were standardized as doxorubicin-equivalent dose, and alkylating agents were summarized as cyclophosphamide

equivalent dose.[18,19] Treatment decade was categorized as 1970-1979, 1980-1989, or 1990-1999 according to date of cancer diagnosis.

Outcomes

Participants reported age at first occurrence of a wide variety of health outcomes via a series of multi-item, organ system-based questions on the baseline questionnaire, and subsequently on up to four follow-up questionnaires (https://ccss.stjude.org/tools-and-documents/questionnaires). Questionnaires included 130-140 items asking whether participants had been told by a doctor that they had specific medical conditions, with open-ended text responses available for reporting "other conditions" for each organ system. Using previously described methods[20] incorporating the U.S. National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v4.03) structure and grading criteria, chronic conditions were categorized as mild (grade 1), moderate (grade 2), severe or disabling (grade 3), life-threatening (grade 4), or fatal (grade 5) (appendix pp. 13-14). Outcome assessment was based on self-report, but self-reported conditions were reviewed and CTCAE categorization was adjudicated by an expert panel of physicians. When available information was insufficient to distinguish between two grades, the lower severity grade was assigned. Because questionnaires captured the age at first occurrence for each condition, multiple occurrences of the same condition were not ascertained, with the exception of subsequent neoplasms. Subsequent neoplasms reported by questionnaire or identified by National Death Index (NDI) searches were confirmed by review of pathology reports and/or medical records. Fatal conditions were ascertained by cause of death information from an NDI search through December 31, 2013.

Statistical analysis

The cumulative incidence of any grade 3-5 chronic condition by time since diagnosis was compared across treatment decades for survivors, with the primary comparison based on Wald tests between cumulative incidence estimates at 20 years post-diagnosis. This was the longest follow-up interval that allowed similar follow-up times for each diagnosis decade. Cancer diagnosis-specific comparisons were based on 15-year cumulative incidence because smaller sample sizes for some diagnoses yielded relatively few survivors at risk beyond 15 years of follow-up, resulting in wide confidence intervals. A sensitivity analysis examined trends across five-year diagnosis intervals. Follow-up time was censored at the most recent CCSS questionnaire, and deaths due to primary cancer recurrence or external causes were treated as competing risks. Conditions that occurred after diagnosis but prior to study entry at 5-years post-diagnosis were included in cumulative incidence estimates as prevalent conditions at the 5-year point. To generate an age-matched cumulative incidence curve among siblings, their follow-up time began at the age at which their related survivor reached 5-years post-diagnosis. For incident conditions among survivors 5-15 years post-diagnosis, diagnosis-specific Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for developing a first grade 3-5 condition, comparing across decades using a linear variable with one unit increase between decades. Follow-up was restricted to 15 years post-diagnosis to ensure adequate sample size throughout follow-up and comparable follow-up across diagnosis decade groups. Models were adjusted for sex and attained age (time-dependent restricted cubic spline). We tested interactions of sex and

race/ethnicity with treatment decade in diagnosis-specific models, and generated stratified results based on those with significant interactions ($p<0.10$). Due to inclusion of only 5-year survivors in the CCSS, time-to-event models were not appropriate for examining prevalent conditions at study entry. Therefore, we examined these conditions separately using cross-sectional Poisson regression models with robust standard errors to estimate prevalence ratios (PRs) and 95% CIs per increasing diagnosis decade.[21] Sampling weights were applied using inverse probability weighting to account for strategic under-sampling of survivors of acute lymphoblastic leukemia diagnosed from 1987-1999.

We hypothesized that changes in the incidence of grade 3-5 chronic conditions across treatment decades may have been partially mediated by changes in treatment that occurred between 1970 and 1999. To examine whether the data was consistent with this hypothesis, we used previously described mediation analysis methods[22-24] under a single mediator model, as shown in the appendix (p. 1). The initial steps of the analysis examined whether there was 1) a significant association between the independent variable (decade) and the dependent variable (rate of grade 3-5 chronic conditions); and 2) a significant association between the independent variable and the mediator (treatment variables). In diagnosis groups that met these criteria, we then estimated hazard ratios for the association between diagnosis decade and rate of chronic conditions in Cox regression models with and without inclusion of relevant treatment variables. Models in which inclusion of treatment variables attenuated the association (resulted in a hazard ratio closer to 1.0), were considered to be consistent with the hypothesis of mediation by treatment. Nonparametric bootstrap was used to statistically test the difference between hazard ratios for decade between models with and without treatment variables. Relevant treatment variables for each diagnosis were identified based on documented changes in treatment protocols over time and expert opinion from oncologists. For analyses examining treatment doses, 1909 individuals with unavailable treatment data were excluded (appendix p. 15). SAS version 9.4 was used for all analyses.

Role of the funding source

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

RESULTS

Population characteristics

The cohort included 23,601 five-year survivors (66% of all eligible; appendix p. 2) and 5,051 siblings (62% of all eligible; appendix p. 3). Among survivors, 6,223 were diagnosed in 1970-1979, 9,420 in 1980-1989, and 7,958 in 1990-1999 (Table 1). The median follow-up time for all survivors was 21 years (interquartile range, IQR, 15-25), and median follow-up by decade of diagnosis was 29 years (IQR 24-33) for 1970-1979, 22 years (IQR 18-24) for 1980-1989, and 15 years (IQR 13-18) for 1990-1999. The overall median age at diagnosis was 6 years (IQR 3-13) and median age at last follow-up was 28 years (IQR 22-35). Among baseline participants, outcome data was missing due to non-participation in follow-up questionnaires for 799 (4%) of 19,033 survivors at 15 years post-diagnosis (excluding those

who had died or had not reached 15 years post-diagnosis at the time of the questionnaire) and for 2116 (14%) of 15,008 survivors at 20 years post-diagnosis (appendix pp. 16-17). The proportion of survivors treated with radiation decreased by decade of diagnosis. Conversely, the proportion of survivors treated with anthracyclines, alkylating agents or platinum compounds increased over time, though cumulative doses were generally reduced from the 1980s to 1990s. Notably, temporal trends in treatment exposures varied by primary cancer diagnosis (appendix pp. 18-21).

Incidence of grade 3-5 chronic conditions

The 20-year cumulative incidence of a grade 3-5 chronic condition decreased significantly from 33·2% (95% CI, 32·0%-34·3%) in survivors diagnosed in the 1970s to 29·3% (95% CI, 28·4%-30·2%, p<0·0001) in the 1980s, and 27·5% (95% CI, 26·4%-28·6%, p=0·012 vs. 1980s) in the 1990s (Figure 1a). In comparison, age-matched 20-year cumulative incidence in all siblings was 4·6% (95% CI, 3·9%-5·2%). Cumulative incidence estimates among siblings did not show clear patterns across the decades of their related survivor's diagnosis (appendix p. 22). The cumulative incidence of two or more grade 3-5 conditions was similar across diagnosis decades (Figure 1b), although a small decrease emerged by 20 years post-diagnosis for survivors diagnosed in the 1990s (8·9%, 95% CI 8·1%-9·6%) compared to the 1970s (9·9%, 95% CI 9·1%-10·6%, p=0·061).

Incidence patterns of grade 3-5 chronic conditions by treatment decade varied across cancer diagnosis groups (Figure 2; appendix p. 23). Patterns were similar when examined using 5-year diagnosis intervals (appendix p. 24). Cumulative incidence by 15 years post-diagnosis was lower for survivors diagnosed 1990-1999 compared to 1970-1979 for survivors of Hodgkin lymphoma (17·7% vs. 26·4%, p<0·0001), non-Hodgkin lymphoma (16·9% vs. 23·8%, p=0·0053), astrocytoma (30·5% vs. 47·3%, p<0·0001), Wilms tumor (11·9% vs. 17·6%, p=0·034), soft tissue sarcoma (28·3% vs. 36·5%, p=0·021), and osteosarcoma (65·6% vs. 87·5%, p<0·0001). In contrast, the 15-year cumulative incidence of a grade 3-5 chronic condition was higher for more recently diagnosed survivors of medulloblastoma/PNET (58·9% for 1990-1999 vs. 42·9% for 1970-1979, p=0·00060) and neuroblastoma (25·0% for 1990-1999 vs. 18·0% for 1970-1979, p=0·0045). In these comparisons of conditions from 0-15 years post-diagnosis, no significant differences in cumulative incidence between diagnosis decades were found for survivors of acute lymphoblastic leukemia (ALL), acute myeloid leukemia, or Ewing sarcoma. Diagnosis-specific temporal patterns for cumulative incidence of two or more grade 3-5 conditions were generally similar to those for a first condition (appendix pp. 4-9, 25), with the exception of an increase from 1970-79 to 1980-89 among survivors of osteosarcoma. Differences by diagnosis decade were more prominent among female survivors compared to males. In diagnosis-specific analyses, a significant interaction between decade and sex (p=0.046) was found among Hodgkin lymphoma survivors (appendix pp. 10-11). Patterns were similar by race/ethnicity (appendix p. 12).

Impact of temporal changes in treatment

After adjustment for sex and attained age, rates of incident grade 3-5 chronic conditions from 5-15 years post-diagnosis decreased significantly across treatment decades for survivors of ALL, Hodgkin lymphoma, non-Hodgkin lymphoma, astrocytoma, and Wilms

tumor (Figure 3; appendix p. 26). As shown in Figure 3, inclusion of treatment variables in the multivariable model attenuated the association between diagnosis decade and rate of incident chronic conditions, consistent with mediation, in all of these groups. However, statistically significant mediation was identified only in survivors of astrocytoma (p=0.0085) and Hodgkin lymphoma (p=0.024), with evidence suggestive of mediation among non-Hodgkin lymphoma survivors (p=0.088) (appendix p. 27). Models examining prevalent conditions at 5 years post-diagnosis yielded similar patterns, with the exception of ALL and Wilms tumor, where there was no decrease in prevalence across treatment decades (appendix p. 26). For survivors of medulloblastoma/PNET and neuroblastoma, there were no associations between treatment decade and rate of incident conditions 5-15 years post-diagnosis, but prevalent conditions that occurred between diagnosis and 5 years post-diagnosis increased for each successive decade among medulloblastoma/PNET (PR, 1·20; 95% CI, 1·08-1·32) and neuroblastoma (PR, 1·30; 95% CI, 1·16-1·44) survivors. Inclusion of treatment variables in the multivariable model attenuated the association for neuroblastoma but not for medulloblastoma/PNET survivors.

The overall decrease in incidence of chronic conditions over time was in part due to a substantial reduction of endocrinopathies (Table 2), from a 15-year cumulative incidence of 5·9% (95% CI, 5·3%-6·4%) in survivors diagnosed 1970-1979 to 2·8% (95% CI, 2·5%-3·2%) in those diagnosed 1990-1999 (p<0·0001). Specifically, there were marked decreases in the incidence of thyroid abnormalities requiring surgery and gonadal dysfunction. Significant decreases over time were also found for second malignant neoplasms, musculoskeletal conditions, and gastrointestinal conditions. In contrast, the cumulative incidence of hearing loss increased substantially over treatment decades (p<0·0001). A modest but statistically significant increase was also found for renal conditions. Examination of prevalence ratios (0-5 years post-diagnosis) and hazard ratios (5-15 years post-diagnosis) yielded similar patterns (appendix p. 28).

DISCUSSION

In this study, 5-year survivors of childhood cancer diagnosed and treated in more recent decades had an overall lower risk of severe, disabling, life-threatening, or fatal chronic health conditions by 20 years post-diagnosis. Treatments for childhood cancer have evolved in recent decades, with the goal of maximizing cure rates while minimizing the adverse effects of therapy. Increased understanding of cancer biology, along with improvements in prediction of tumor response and disease progression, enabled risk-stratification of therapeutic approaches. In general, radiation volumes have been decreased for most patients, and radiation doses have been decreased through increased use of chemotherapy.[7,8] Particularly for children with low-risk disease, further modifications have reduced cumulative dosages of chemotherapeutic agents. Concurrently, treatment intensity has increased for those with high-risk disease to further improve survival.[7,8] The results of this study are consistent with a decrease in mortality attributable to the late effects of treatment over the same time period,[11] providing further support that treatment modifications were associated with overall improvements in late health outcomes for survivors. However, heterogeneity of the results according to diagnosis group highlights the importance of considering specific differences in treatment and survival patterns over time.

A notable commonality among diagnoses for which the incidence of chronic conditions decreased in more recent treatment decades, with the exception of osteosarcoma, was a reduction in the use and/or maximum dosages of radiation therapy in more recently treated survivors (appendix pp. 18-21). Reductions in radiation exposure were concomitant with increased use of chemotherapeutic agents such as alkylating agents and anthracyclines, although cumulative dosages of these drugs generally declined over time. The results of mediation analysis were consistent with treatment changes as a partial mediating factor for the association between diagnosis decade and risk of grade 3-5 conditions for survivors of astrocytoma, Hodgkin lymphoma and non-Hodgkin lymphoma, but not for Wilms tumor. Further research is needed to determine the factors underlying the reduced incidence of serious chronic conditions in more recently treated Wilms tumor survivors.

A significant decrease in the cumulative incidence of a first grade 3-5 condition across treatment decades was also found for survivors of osteosarcoma, primarily due to a decrease in prevalent conditions at the time of five-year survival. However, the incidence of multiple serious chronic conditions actually increased for survivors treated more recently, possibly because osteosarcoma survivors in CCSS diagnosed 1990-1999 had greater exposure to alkylating agents, anthracyclines, and platinum compounds compared to those diagnosed earlier. The temporal decreases in chronic conditions developing early after diagnosis may reflect improvements in surgical treatment and medical management, which we were unable to evaluate.

Paradoxically, our results showing increased incidence of serious chronic conditions in more recently treated survivors of medulloblastoma and neuroblastoma may be a byproduct of the success of treatment changes over this time period. In neuroblastoma, for example, improvements in disease risk stratification enabled distinct treatment patterns for patients with low-risk versus high-risk disease.[7] Studies during the 1980s demonstrated that localized neuroblastoma with favorable biological features could be effectively treated without radiation or chemotherapy, along with reduced radiation for patients with regional low-risk disease.[25,26] Concurrently, intensified therapy for patients with high-risk disease, including use of aggressive multi-agent chemotherapy, autologous stem cell transplantation, and isotretinoin contributed to increasing five-year survival rates among this group.[27] Due to these temporal trends in survival, more survivors of high-risk neuroblastoma exposed to intensive treatments were likely eligible to participate in CCSS from 1990-1999 compared to earlier decades, potentially contributing to the temporal increase in the prevalence of grade 3-5 chronic conditions within five years of diagnosis. The CCSS does not include information on risk-stratification classifications for primary cancer diagnoses. Inclusion of more high-risk patients in CCSS in more recent decades due to increased survival rates in this subgroup likely contributed to the temporal increase in grade 3-5 condition incidence among survivors of medulloblastoma/PNET as well. Notably, these survivors also had the highest incidence of two or more grade 3-5 conditions by 15 years post-diagnosis.

The most prominent reduction in the incidence of chronic diseases was observed for endocrinopathies, particularly gonadal dysfunction, for which increased risk has been associated with abdominal/pelvic radiation, cranial radiation affecting the hypothalamic-pituitary axis, and high cumulative doses of alkylating agents.[28] In previous CCSS analyses,

temporal reductions in rates of subsequent malignant neoplasms were largely attributed to reductions in the use, dose, and size of fields of radiation therapy.[24] In contrast to these temporal reductions, the incidence of hearing loss was twice as high in survivors diagnosed in 1990-1999 compared to 1970-1979. Although the proportion of survivors exposed to craniospinal radiation decreased over this time period, there was a concurrent increase in exposure to platinum agents, which have been associated with ototoxicity and irreversible hearing loss.[29]

To our knowledge, our results provide the most comprehensive and quantitative assessment to date of temporal trends in late effects among a cohort of childhood cancer survivors over a period in which treatment regimens evolved substantially for many diagnoses. While advances in knowledge of the underlying pathobiology of cancers and further recognition of the late effects of treatments have spurred continued evolution of childhood cancer treatments in the 21st century, the experiences of survivors diagnosed through 1999 remain relevant to recently diagnosed patients because radiation and conventional chemotherapeutic agents remain integral parts of therapy for most cancers. Current treatment regimens for osteosarcoma and ALL, for example, are similar to those employed in the 1990s. However, the CCSS cohort does not include appreciable numbers of participants treated with newer radiation modalities, such as intensity-modulated radiation therapy (IMRT) or proton therapy, or targeted biological agents such as tyrosine kinase inhibitors or immunotherapy. Thus, long-term follow-up of contemporary patients will be critical to augment these findings and continue to inform survivorship care.

The combination of large sample size, detailed annotation of treatment data, and lengthy follow-up of survivors diagnosed over three decades in the CCSS provides unique evidence of temporal reductions in the incidence of grade 3-5 chronic health conditions among a substantial number of pediatric cancer diagnoses. However, these findings need to be considered in the context of some limitations. The analysis focused on grade 3-5 chronic conditions because survivors are likely to report serious health problems accurately, but ascertainment of outcomes via self-report may result in misclassification. Selection bias resulting from incomplete participation in CCSS among eligible survivors is possible. Notably, participant characteristics were similar across treatment decades and prior reports have shown that CCSS participants and non-participants are similar with respect to demographic and cancer characteristics.[15,16] Moreover, it has previously been shown that CCSS participants are representative of the U.S. childhood cancer survivor population.[30] The CCSS only included survivors of the most common childhood cancer diagnoses, so some less common diagnoses, such as retinoblastoma, hepatoblastoma and germ cell tumors are not represented. Advances in risk-adapted therapy have occurred for these diagnoses as well, but specific studies of these survivors would be required to examine the balance between reduced therapeutic intensity for low-risk disease and improved survival of high-risk patients treated with intensive therapy. Examinations of incidence of two or more grade 3-5 conditions per participant were limited to different condition types, as only the first occurrence of a condition was ascertained. Ascertainment of chronic health conditions may be more complete in survivors compared to siblings due to increased medical surveillance. Finally, we were unable to examine the role of other temporal patterns such as changes in

health care and medical surveillance that may also have contributed to the observed chronic disease patterns.

Our results provide important evidence that, overall, childhood cancer survivors treated in more recent decades have a lower incidence of serious chronic conditions. This reduced risk parallels reductions in treatment intensity over the same time period, providing support that efforts by oncologists to modify childhood cancer treatment regimens by reducing therapeutic intensity in suitable patients were associated with improved late health outcomes. Yet, despite meaningful progress, reductions in these late effects were modest, and our results indicate important variability by diagnosis and type of chronic condition that may inform further treatment modifications as well as follow-up care of more recently treated survivors. Additional analyses within the CCSS cohort will be able to expand on these results with more in-depth examinations of specific therapeutic regimens and condition types within diagnosis groups. Ongoing efforts to further modify treatments offer promise of continued progress in reducing late effects, but the primary goal of achieving a cure continues to come at a cost for many survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

Evidence before this study

Survivors of childhood cancer have increased risks for morbidity and mortality due to the late effects of cancer therapy, and recognition of these increased risks has resulted in modifications to treatment regimens with the goals of improving cure rates while reducing the risk and severity of late effects. We searched PubMed from database inception until April 12, 2018, using the search terms “childhood cancer” and “survivor” and (“late effect” or “chronic condition” or “health” or “mortality” or “morbidity”) and (“trend” or “temporal” or “pattern” or “change” or “era”) to identify studies that included an examination of temporal changes in the incidence or burden of morbidity among survivors of childhood cancer. We additionally examined the bibliographies of selected references. A number of large and robust cohort analyses, including from the Childhood Cancer Survivor Study (CCSS), British Childhood Cancer Survivor Study, and the Nordic countries, have examined temporal trends in mortality among survivors. There have also been specific analyses of temporal trends in incidence of subsequent neoplasms, but survivors have increased risk for a wide range of chronic conditions impacting numerous organ systems. To our knowledge, there have been no comprehensive analyses of temporal trends in treatment and subsequent development of serious chronic health conditions in a large and extensively characterized population of childhood cancer survivors.

Added value of this study

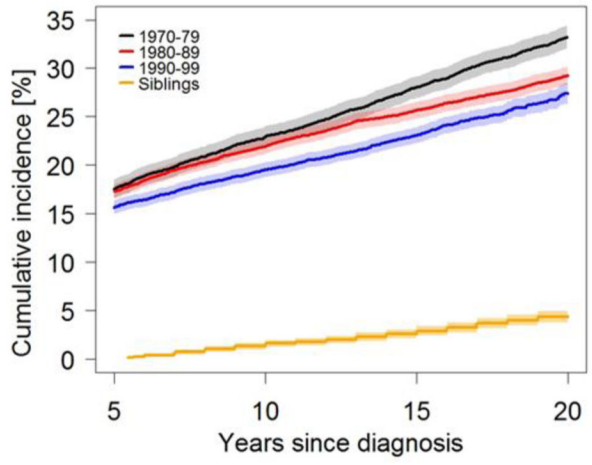
Prior studies have demonstrated reduced mortality from late effects of treatment among more recently diagnosed childhood cancer survivors, but optimum survivorship should include both extended lifespan and improvements in overall health. A previous CCSS analysis found that self-reported health status was actually reduced in more recently diagnosed survivors, so our study addresses the critical question of whether temporal trends in serious morbidity are consistent with previously identified reductions in mortality. Changes in treatment over time have been heterogeneous with respect to cancer diagnosis, so this study is notable as the first comprehensive examination of diagnosis-specific temporal trends in severe, disabling, life-threatening, or fatal chronic health conditions in a large cohort of survivors with detailed treatment exposure data. Our findings show that when considered in aggregate 5-year survivors of childhood cancer diagnosed and treated in more recent decades had an overall lower risk of serious chronic health conditions by 20 years post-diagnosis, providing further support that treatment modifications were associated with overall improvements in late health outcomes for survivors. However, improvements were not uniform across diagnosis groups or condition types, highlighting differences in treatment and survival patterns over time.

Implications of all the available evidence

Treatments for childhood cancer have evolved in recent decades, with improvements in risk stratification enabling reduced treatment intensities for those with low-risk disease, while those with high-risk disease receive treatments directed at increasing survival, which generally consist of more intense therapy and/or addition of new agents. While

these treatment changes were associated with improvements in late health outcomes for survivors overall, reductions in occurrence of serious chronic conditions have been modest and subgroups of survivors continue to experience high rates of morbidity. Treatments for pediatric malignancies are continually evolving, which requires ongoing research to monitor the short- and long-term impact of these changes on risk of late effects. Both survivors and health care providers should be aware of the health risks associated with specific cancer diagnoses and treatment exposures in order to counsel survivors and provide optimal clinical follow-up.

A.



20-Year Cumulative Incidence (95% CI)

1970-79: 33.2% (32.0-34.3)

1980-89: 29.3% (28.4-30.2)

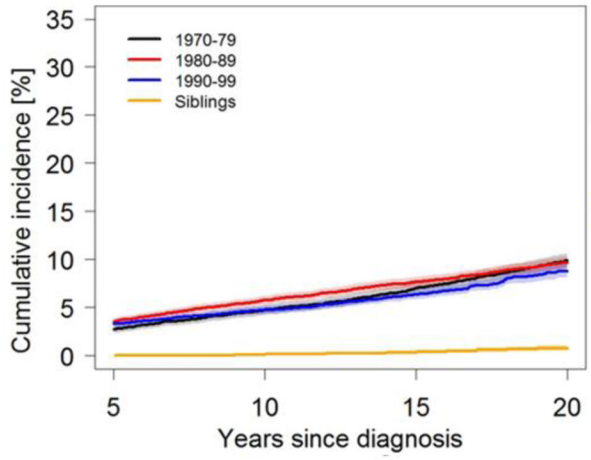
1990-99: 27.5% (26.4-28.6)

Siblings: 4.6% (3.9-5.2)

Number at Risk by Time Since Diagnosis

	5 years	10 years	15 years	20 years
Survivors 1970-79	6197	4546	4152	3611
Survivors 1980-89	9373	6948	6009	4698
Survivors 1990-99	7929	5942	3471	702
Siblings	4905	4772	4355	3492

B.



20-Year Cumulative Incidence (95% CI)

1970-79: 9.9% (9.1-10.6)

1980-89: 9.7% (9.1-10.3)

1990-99: 8.9% (8.1-9.6)

Siblings: 0.8% (0.5-1.1)

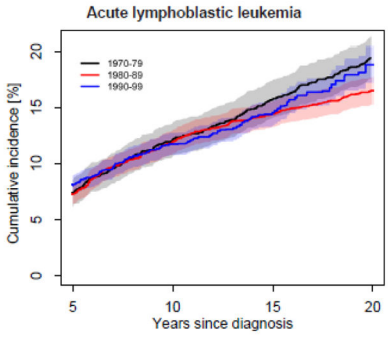
Number at Risk by Time Since Diagnosis

	5 years	10 years	15 years	20 years
Survivors 1970-79	6222	5606	5328	4809
Survivors 1980-89	9420	8421	7462	6036
Survivors 1990-99	7956	7167	4251	872
Siblings	5046	4966	4582	3734

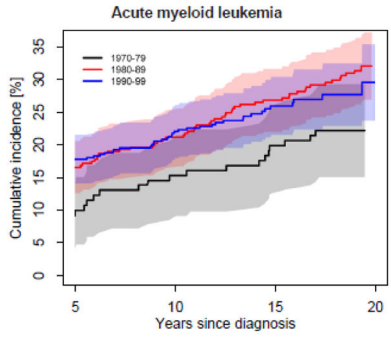
Figure 1:

Cumulative incidence of grade 3-5 chronic health conditions in 5-year survivors of childhood cancer, by diagnosis decade, and siblings. **Panel A** shows the cumulative incidence of a first grade 3-5 condition. The cumulative incidence of a grade 3-5 condition decreased significantly comparing 1970-79 vs. 1980-89 (p<0·0001), 1980-89 vs. 1990-99 (p=0·012), and 1970-79 vs. 1990-99 (p<0·0001). **Panel B** shows the cumulative incidence of two or more grade 3-5 conditions. The cumulative incidence of at least two grade 3-5 conditions decreased significantly only for the comparison between 1970-79 vs. 1990-99,

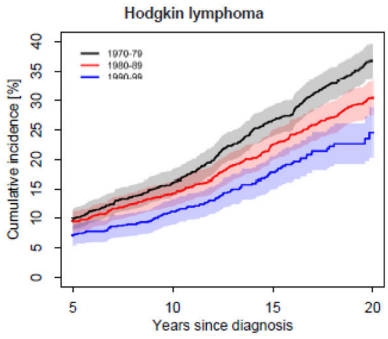
but the decrease was not significant (p=0·061).The shaded area represents the 95% confidence interval. The number of participants at risk (number censored) at each 5-year interval post-diagnosis is listed below the x-axis. The number censored does not include those who experienced a competing risk event (death from a cause other than a grade 5 chronic condition)



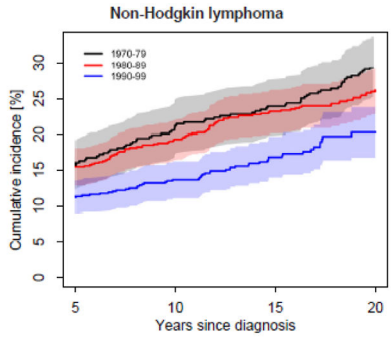
1970-1979	1820	1489	1399	1259
1980-1989	2885	2422	2117	1660
1990-1999	1431	1181	707	131



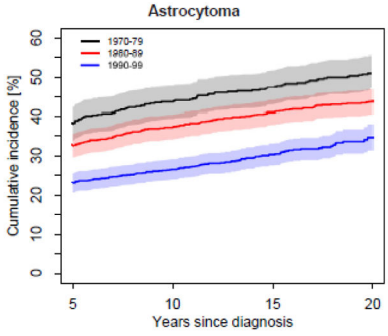
1970-1979	131	104	94	84
1980-1989	327	246	213	170
1990-1999	400	306	170	23



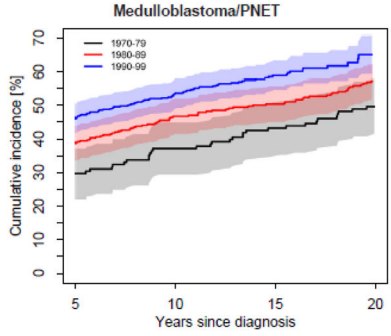
1970-1979	1091	877	752	596
1980-1989	1055	876	727	551
1990-1999	841	726	389	70



1970-1979	451	349	333	289
1980-1989	769	599	518	408
1990-1999	697	588	367	85



1970-1979	505	272	247	218
1980-1989	937	564	484	378
1990-1999	1134	805	482	112



1970-1979	148	81	71	57
1980-1989	347	175	143	105
1990-1999	498	224	113	18

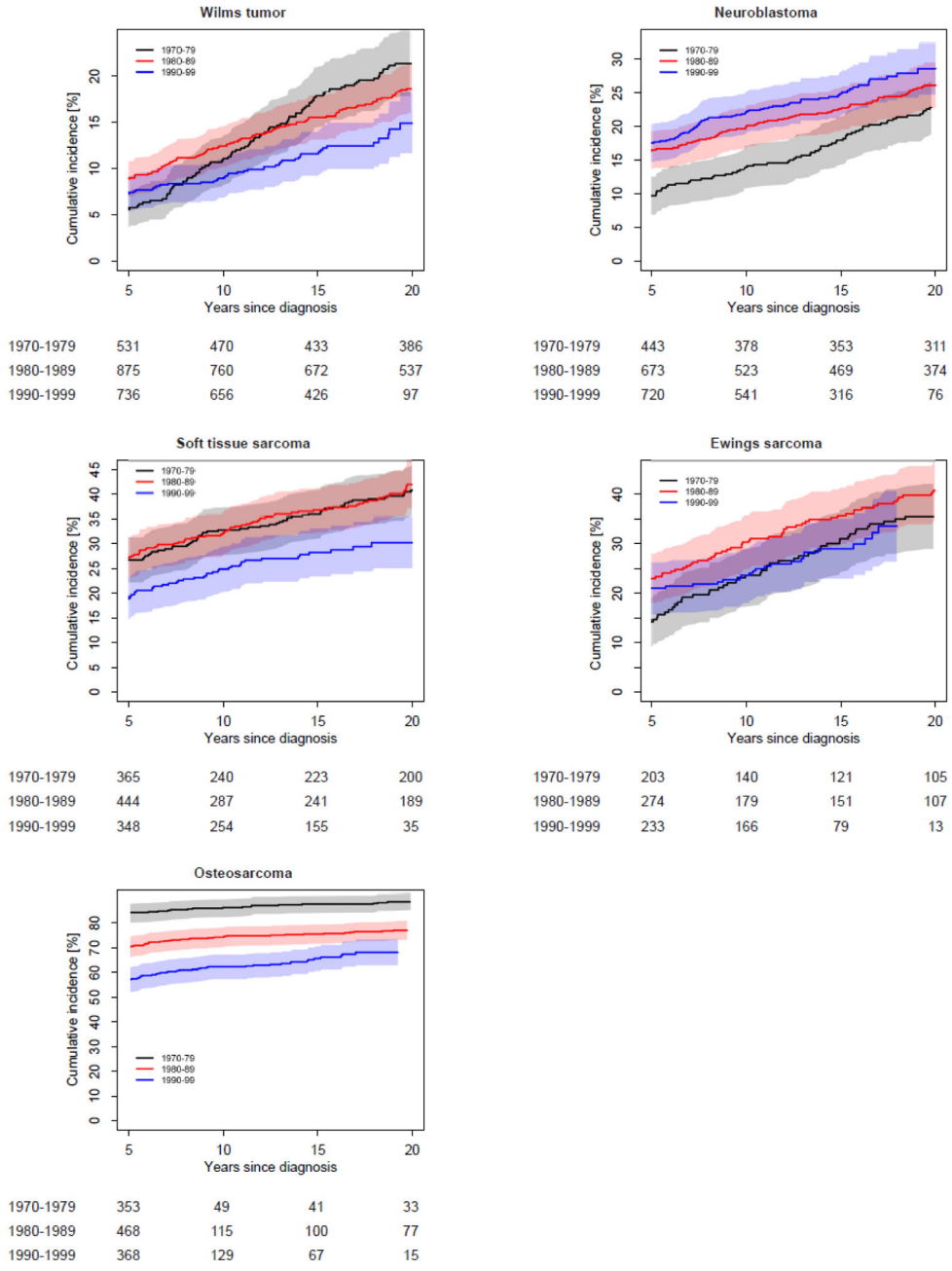


Figure 2:

Diagnosis-specific cumulative incidence of a first grade 3-5 chronic condition by diagnosis decade. The shaded area represents the 95% confidence interval. The number of participants at risk (number censored) at each 5-year interval post-diagnosis is listed below the x-axis. The number censored does not include those who experienced a competing risk event (death from a cause other than a grade 5 chronic condition)

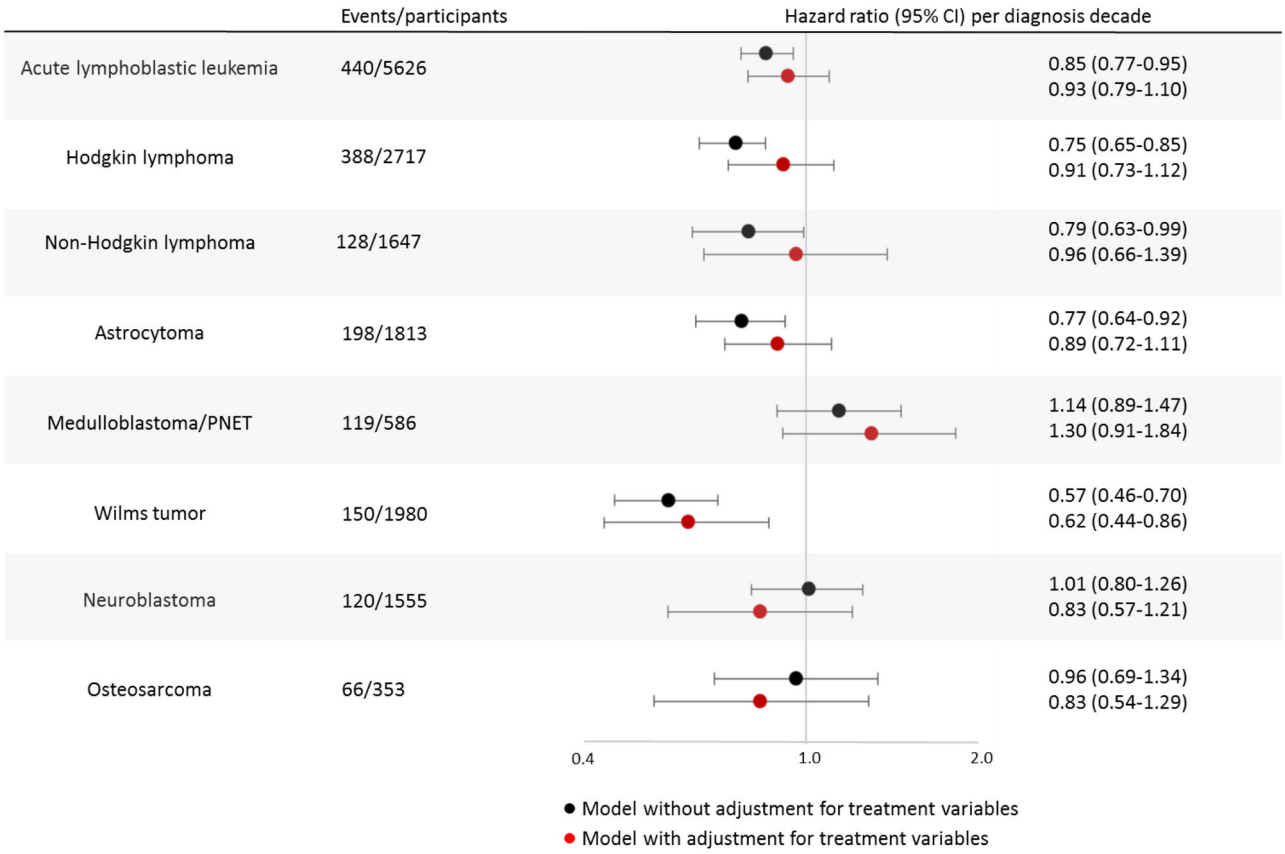


Figure 3.

Incident grade 3-5 chronic conditions that occurred between study entry (5 years postdiagnosis) and 15 years post-diagnosis were examined in multivariable Cox regression models that included diagnosis decade as a linear variable with one unit increase between decades. The black circle represents the hazard ratio for each one decade increase in diagnosis decade in a multivariable model including sex and attained age as a cubic spline. The red circle represents the hazard ratio in the same model, but with the addition of diagnosis-specific treatment variables. Treatment variables included in each model are detailed in the appendix (pp. 29-30).

Table 1:

Descriptive characteristics of 23,601 childhood cancer survivors by diagnosis decade and 5,051 siblings

				Diagnosis Decade							
		All survivors		1970-1979		1980-1989		1990-1999		Siblings	
		N	%	N	%	N	%	N	%	N	%
Sex	Female	10947	46·4	2900	46·6	4321	45·9	3726	46·8	2643	52·3
	Male	12654	53·6	3323	53·4	5099	54·1	4232	53·2	2408	47·7
Race/ethnicity	Non-Hispanic White	19346	82·4	5533	89·2	7796	83·1	6017	76·0	4377	89·7
	Non-Hispanic Black	1500	6·4	241	3·9	577	6·2	682	8·6	151	3·1
	Hispanic	1784	7·6	292	4·7	616	6·6	876	11·1	214	4·4
	Other	862	3·7	135	2·2	388	4·1	339	4·3	140	2·9
Age at diagnosis	0-9 years	14811	62·8	3830	61·5	6111	64·9	4870	61·2	·	·
	10-20 years	8790	37·2	2393	38·5	3309	35·1	3088	38·8	·	·
Age at last follow-up/death	<20 years	3954	16·8	402	6·5	1120	11·9	2432	30·6	419	8·3
	20-29 years	9293	39·4	953	15·3	4354	46·2	3986	50·1	1591	31·5
	30-39 years	7257	30·7	2651	42·6	3088	32·8	1518	19·1	1734	34·3
	40-49 years	2693	11·4	1816	29·2	855	9·1	22	0·3	1047	20·7
	≥50 years	404	1·7	401	6·4	3	0·0	0	0·0	260	5·1
Diagnosis	Acute lymphoblastic leukemia	6148	26·0	1824	29·3	2892	30·7	1432	18·0	·	·
	Acute myeloid leukemia	866	3·7	131	2·1	333	3·5	402	5·1	·	·
	Other leukemia[1]	303	1·3	74	1·2	105	1·1	124	1·6	·	·
	Astrocytomas	2594	11·0	509	8·2	945	10·0	1140	14·3	·	·
	Medulloblastoma, PNET	997	4·2	148	2·4	349	3·7	500	6·3	·	·
	Other CNS tumors[2]	645	2·7	79	1·3	206	2·2	360	4·5	·	·
	Hodgkin lymphoma	2996	12·7	1097	17·6	1057	11·2	842	10·6	·	·
	Non-Hodgkin lymphoma	1932	8·2	453	7·3	774	8·2	705	8·9	·	·
	Wilms tumor	2148	9·1	534	8·6	877	9·3	737	9·3	·	·
	Neuroblastoma	1838	7·8	443	7·1	674	7·2	721	9·1	·	·
	Soft tissue sarcoma	1162	4·9	365	5·9	448	4·8	349	4·4	·	·
	Ewing sarcoma	714	3·0	203	3·3	277	2·9	234	2·9	·	·
	Osteosarcoma	1205	5·1	360	5·8	474	5·0	371	4·7	·	·
	Other bone tumors[3]	53	0·2	3	0·0	9	0·1	41	0·5	·	·
Radiation	None	9275	43·1	1219	22·6	3588	42·5	4468	58·1	·	·
	Any site	12245	56·9	4163	77·4	4855	57·5	3227	41·9	·	·
	Chest	5393	25·4	1737	33·2	1975	23·8	1681	21·9	·	·
	Brain/spine	6497	30·6	2030	38·8	2734	33·0	1733	22·5	·	·
	Abdomen	5112	24·1	1723	32·9	1837	22·2	1552	20·2	·	·
	Pelvis	4234	20·0	1390	26·5	1527	18·4	1317	17·1	·	·
Alkylating agents	None	9747	48·7	2793	58·5	3663	46·4	3291	44·7	·	·
(cyclophosphamide equivalent dose)	Any	10287	51·3	1978	41·5	4236	53·6	4073	55·3	·	·
	1<4000 mg/m^2	2563	12·8	341	7·1	1193	15·1	1029	14·0	·	·

				Diagnosis Decade							
		All survivors		1970-1979		1980-1989		1990-1999		Siblings	
		N	%	N	%	N	%	N	%	N	%
	4000-<8000 mg/m^2	2641	13·2	406	8·5	1045	13·2	1190	16·2	·	·
	8000-<12000 mg/m^2	2093	10·4	396	8·3	886	11·2	811	11·0	·	·
	12000-<16000 mg/m^2	1191	5·9	301	6·3	545	6·9	345	4·7	·	·
	16000-<20000 mg/m^2	684	3·4	207	4·3	284	3·6	193	2·6	·	·
	≥20000 mg/m^2	1115	5·6	327	6·9	283	3·6	505	6·9	·	·
Anthracyclines (doxorubicin equivalent dose)	None	11198	53·6	3721	72·0	4262	52·2	3215	42·6	·	·
	Any	9676	46·4	1445	28·0	3904	47·8	4327	57·4	·	·
	1<100 mg/m^2	1395	6·7	118	2·3	552	6·8	725	9·6	·	·
	100-<250 mg/m^2	4013	19·2	354	6·9	1366	16·7	2293	30·4	·	·
	250-<400 mg/m^2	2889	13·8	490	9·5	1404	17·2	995	13·2	·	·
	≥400 mg/m^2	1379	6·6	483	9·3	582	7·1	314	4·2	·	·
Epipodophyllotoxins	None	17579	82·9	5251	97·9	7174	86·3	5154	68·5	·	·
	Any	3618	17·1	115	2·1	1137	13·7	2366	31·5	·	·
	1<100 mg/m^2	31	0·1	·	·	7	0·1	24	0·3	·	·
	≥100 mg/m^2	3587	16·9	115	2·1	1130	13·6	2342	31·1	·	·
Platinums	None	19080	89·3	5332	98·9	7608	90·6	6140	81·0	·	·
	Any	2289	10·7	58	1·1	787	9·4	1444	19·0		
	1<300 mg/m^2	466	2·2	17	0·3	176	2·1	273	3·6	·	·
	≥300 mg/m^2	1823	8·5	41	0·8	611	7·3	1171	15·4	·	·

Note: % reported among non-missing; # with unknown values: n=278 race, n=1909 survivors did not provide consent for release of medical records (Supplemental Table S2); additionally missing: n=172 radiation, 483 chest RT,476 CNS RT,483 abdomen RT,482 pelvis RT, 1658 CED dose, 818 anthracycline dose, 495 epipodophyllotoxin dose, 219 bleomycin dose, 323 platinum dose.

[1]Other leukemias (with more than 3 cases): leukemia, NOS (n=40); acute leukemia, NOS (n=59); prolymphocytic leukemia, NOS (n=16); adult T-cell leukemia/lymphoma, HTLV-1 positive (n=17); sub-acute myeloid leukemia (n=18); chronic myeloid leukemia, NOS (n=124); chronic myelomonocytic leukemia, NOS (n=4); myelodysplastic syndrome, NOS (n=8)

[2]Other CNS tumors (with more than 3 cases): pineoblastoma (n=21); subependymal giant cell astrocytoma (n=23); choroid plexus carcinoma (n=27); ependymoma, NOS (n=331); ependymoma, anaplastic (n=34); papillary ependymoma (n=5); myxopapillary ependymoma (n=16); oligodendroglioma, NOS (n=107); oligodendroglioma, anaplastic (n=5); ganglioglioma, NOS (n=75)

[3]Other bone tumors (with more than 3 cases): peripheral neuroectodermal tumor (n=52)

Table 2.

Cumulative incidence of grade 3-5 chronic health conditions by organ system at 15 years after primary cancer diagnosis among 5-year survivors

Chronic Conditions by Organ System	1970-1979 Cumulative Incidence % (95% CI)	1980-1989 Cumulative Incidence % (95% CI)	1990-1999 Cumulative Incidence % (95% CI)	P-Values		
				1980s vs. 1970s	1990s vs. 1970s	1990s vs. 1980s
Endocrine	5·9 (5·3-6·4)	3·6 (3·2-3·9)	2·8 (2·5-3·2)	<0·0001	<0·0001	0·0033
Thyroid nodules requiring surgery	1·9 (1·6-2·3)	1·2 (0·9-1·4)	0·9 (0·7-1·1)	0·00017	<0·0001	0·10
Gonadal dysfunction	3·5 (3·1-4·0)	1·8 (1·5-2·1)	0·9 (0·7-1·0)	<0·0001	<0·0001	<0·0001
Diabetes mellitus requiring insulin	0·4 (0·2-0·5)	0·5 (0·3-0·6)	0·9 (0·7-1·0)	0·35	0·00014	0·0015
2nd Malignant Neoplasms	2·7 (2·3-3·1)	2·4 (2·1-2·7)	1·9 (1·6-2·2)	0·31	0·0033	0·024
Cardiovascular	4·8 (4·3-5·3)	5·6 (5·2-6·1)	4·9 (4·5-5·3)	0·018	0·74	0·023
Heart failure	0·9 (0·6-1·1)	1·0 (0·8-1·2)	0·8 (0·6-0·9)	0·32	0·49	0·057
Myocardial infarction	0·6 (0·4-0·8)	0·5 (0·4-0·6)	0·4 (0·3-0·5)	0·47	0·14	0·38
Stroke	1·5 (1·2-1·8)	2·4 (2·1-2·7)	2·0 (1·7-2·3)	<0·0001	0·036	0·032
Thromboembolic disease	2·2 (1·8-2·5)	2·1 (1·8-2·4)	2·0 (1·7-2·3)	0·75	0·40	0·54
Neurological	4·8 (4·2-5·3)	5·3 (4·9-5·8)	4·3 (3·9-4·7)	0·10	0·17	0·00058
Memory problems	1·7 (1·4-2·0)	2·5 (2·2-2·8)	2·8 (2·5-3·1)	0·00047	<0·0001	0·24
Balance problems	0·6 (0·4-0·8)	1·0 (0·8-1·2)	1·2 (1·0-1·4)	0·012	<0·0001	0·13
Paralysis	2·7 (2·3-3·1)	2·2 (1·9-2·5)	0·2 (0·1-0·3)	0·059	<0·0001	<0·0001
Hearing Loss	3·0 (2·6-3·5)	4·2 (3·8-4·6)	5·7 (5·2-6·1)	0·00010	<0·0001	<0·0001
Visual impairment	4·5 (4·0-5·0)	4·1 (3·8-4·5)	4·1 (3·7-4·5)	0·34	0·29	0·91
Cataracts requiring surgery	0·8 (0·6-1·1)	1·0 (0·8-1·2)	1·3 (1·1-1·5)	0·18	0·0040	0·084
Blindness	4·0 (3·5-4·5)	3·5 (3·1-3·8)	3·1 (2·8-3·5)	0·11	0·0043	0·14
Gastrointestinal	2·3 (2·0-2·7)	2·3 (2·1-2·6)	1·5 (1·3-1·8)	0·95	0·00037	<0·0001
Intestinal obstruction	2·0 (1·7-2·4)	1·9 (1·7-2·2)	1·1 (0·9-1·3)	0·64	<0·0001	<0·0001
Hepatitis	0·3 (0·2-0·4)	0·4 (0·3-0·5)	0·4 (0·3-0·5)	0·22	0·28	0·88
Musculoskeletal	5·8 (5·2-6·4)	4·4 (4·0-4·7)	3·3 (2·9-3·6)	<0·0001	<0·0001	<0·0001
Amputation	5·1 (4·6-5·6)	2·9 (2·5-3·2)	1·2 (1·0-1·4)	<0·0001	<0·0001	<0·0001
Major joint replacement	0·8 (0·6-1·1)	1·6 (1·4-1·9)	2·2 (2·0-2·5)	<0·0001	<0·0001	0·0015
Respiratory	0·7 (0·5-0·9)	0·5 (0·4-0·7)	0·8 (0·6-0·9)	0·37	0·42	0·051
Pulmonary fibrosis	0·2 (0·1-0·3)	0·3 (0·2-0·4)	0·7 (0·5-0·8)	0·21	<0·0001	0·00078
Renal	0·5 (0·4-0·7)	1·0 (0·8-1·2)	0·9 (0·8-1·1)	0·0010	0·0026	0·75
Dialysis	0·5 (0·3-0·7)	0·9 (0·7-1·1)	0·9 (0·7-1·1)	0·0009	0·0026	0·72