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Long-Term Effects of Radiation Exposure among Adult Survivors of Childhood Cancer: Results from the Childhood Cancer Survivor Study

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Abstract

In the last four decades, advances in therapies for primary cancers have improved overall survival for childhood cancer. Currently, almost 80% of children will survive beyond 5 years from diagnosis of their primary malignancy. These improved outcomes have resulted in a growing population of childhood cancer survivors. Radiation therapy, while an essential component of primary treatment for many childhood malignancies, has been associated with risk of long-term adverse outcomes. The Childhood Cancer Survivor Study (CCSS), a retrospective cohort of over 14,000 survivors of childhood cancer diagnosed between 1970 and 1986, has been an important resource to quantify associations between radiation therapy and risk of long-term adverse health and quality of life outcomes. Radiation therapy has been associated with increased risk for late mortality, development of second neoplasms, obesity, and pulmonary, cardiac and thyroid dysfunction as well as an increased overall risk for chronic health conditions. Importantly, the CCSS has provided more precise estimates for a number of dose–response relationships, including those for radiation therapy and development of subsequent malignant neoplasms of the central nervous system, thyroid and breast. Ongoing study of childhood cancer survivors is needed to establish long-term risks and to evaluate the impact of newer techniques such as conformal radiation therapy or proton-beam therapy.

INTRODUCTION

Over the last four decades, advances in surgical technique, supportive care, radiation delivery and the use of combination chemotherapy have improved survival for childhood cancer. The relative 5-year survival rate, which was less than 30% in 1960, is now 79 % (1). The National Cancer Institute's Office of Cancer Survivorship estimates that as of January 1, 2005, there were over 328,000 survivors of childhood cancer in the United States, including large numbers of survivors of CNS tumors (51,650), acute lymphoblastic leukemia (ALL, 49,271), germ cell tumors (34,169) and Hodgkin lymphoma (31,598) (2). The impact of this growing number of cancer survivors is apparent when one considers that 1 in 900 people in the United States is a survivor of childhood cancer with an estimated 1 in 680 among the population between the ages of 20–50 years.

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The increase in the survival of pediatric cancer patients has created a new and growing population who are at increased risk for adverse outcomes such as late mortality, second neoplasms, organ dysfunction (e.g. cardiac, pulmonary, gonadal), impaired growth and development, decreased fertility, impaired cognitive function, difficulties obtaining employment and insurance, and overall reduction in quality of life (3–13). While causes of poor late outcomes are often multifactorial (including factors related to the primary tumor diagnosis, underlying genetic predisposition, pre-morbid conditions, health behaviors, and host demographic factors such as age, sex and race) it is the treatment (surgery, radiation, chemotherapy) for cancer that is often the most significant contributor. Radiation therapy has been an essential element of treatment of childhood cancer, resulting in improvements in survival for some of the most common malignancies, including childhood ALL (prophylactic cranial irradiation), medulloblastoma (craniospinal radiation therapy), and many solid tumors. However, the increased use of radiation therapy has also resulted in an increase in long-term treatment-related adverse outcomes.

Many of the early insights regarding the long-term effects of radiation therapy occurred in the 1970s and 1980s. For example, cranial radiation therapy was found to be associated with cognitive decline (14) and neck radiation therapy with high rates of hypothyroidism (15,16). Development of subsequent neoplasms was seen within radiation therapy fields (17), and pulmonary and cardiac compromise was found (18,19). The earliest reports of radiation therapy-associated late effects consisted of case series from single institutions or multi-institutional consortia.

Recognizing the limitations imposed by small sample size and lack of long-term follow-up, the CCSS was established to provide a population for comprehensive evaluation of late effects across a broad spectrum of health outcomes. The precise quantification of chemotherapy and radiation dose as well as the heterogeneity of exposures among the CCSS cohort has allowed a more detailed evaluation of risk, within the context of dose–response relationships, for many radiation therapy-related outcomes.

The CCSS, initiated in 1994, represents a retrospective cohort with longitudinal follow-up. Investigation within the cohort has revealed radiation therapy-associated risks for adverse long-term outcomes. The purpose of this review is to highlight some of these findings.

THE CHILDHOOD CANCER SURVIVOR STUDY

Established as an NCI-funded resource, the CCSS is a retrospective cohort of 5-year survivors of childhood cancer from 26 institutions in the United States and Canada (3). Eligibility criteria include cancer diagnosis between January 1, 1970 and December 31, 1986, survival at 5 years from date of diagnosis regardless of disease or treatment status, with restriction to specific diagnoses including leukemia, central nervous system (CNS) cancer, Hodgkin and non-Hodgkin lymphoma, renal tumors, neuroblastoma, soft-tissue sarcomas, and bone tumors. Of the 20,720 eligible survivors identified, 14.6% were lost to follow-up despite extensive tracing efforts. Of those successfully contacted, 81.2% consented for study. To provide a comparison population, a randomly selected cohort of 5,857 siblings (identifying the sibling of nearest age to the CCSS participant) of survivors was identified, and 67% consented for study. Information collected on the sibling cohort, with the exception of cancer-specific topics, was identical to that obtained from the survivor population. Siblings were more likely to be older, female and Caucasian compared to survivors, but absolute differences were relatively small (4). The CCSS was approved by the institutional review board of each participating institution.

Essential to the identification of associations between cancer treatment and long-term health outcomes is precision in exposure assessment (i.e., exposure to cancer therapy). Using trained data management staff, detailed treatment-related information was abstracted from each institutional medical record. This included surgical procedures and chemotherapy administration, with cumulative dose for many chemotherapeutics. For patients who had radiation therapy, the full radiation record from the radiation oncology department was copied and forwarded to M. D. Anderson Cancer Center for review and coding of absorbed doses to specific anatomic sites. Dose estimates were based on measurements in tissue-equivalent phantoms and calculations in a three-dimensional mathematical phantom designed to simulate children of any ages and sizes. Details of the radiation methods are described in Stovall *et al.* (20). Acquisition of such detailed dose and location information in such a large population has allowed CCSS investigators to evaluate a broad range of issues among long-term survivors. Comprehensive reviews of these outcomes have been published (3–13).

SURVIVORS' KNOWLEDGE OF PRIOR RADIATION EXPOSURE

Accurate information regarding previous treatment exposures reflects an important factor for determining appropriate health screening and healthcare delivery (21). While little previous research has occurred on this topic, several studies have documented rates between 77–90% for accurate reporting of cancer history (22,23).

In a cross-sectional study of 635 survivors, the CCSS found that only 72% recalled the correct detailed name of their cancer. Eighty-nine percent of radiation therapy-exposed respondents accurately recalled that they received radiation therapy, while 8% did not know and 3% incorrectly reported that they had not been treated with radiation therapy (24). Among those who had not received radiation therapy, 10% incorrectly reported that they had been treated with radiation therapy. Controlling for other demographic and treatment factors, participants treated at an age <5 years and those with lower educational status (not receiving a high school diploma) were less likely to report their radiation therapy history accurately.

There are many reasons why survivors may report their cancer treatments inaccurately. Some participants may have been too young to understand the significance of such treatment, and in some cases, parents may have elected to “protect” participants from such knowledge. These findings reinforce the fact that a medical history of radiation therapy is not always reported reliably by survivors and should be verified by review of medical records. From a research perspective, reliance on self-report of treatment exposure in studies of long-term outcomes among survivors can result in misclassification with either attenuation of risk estimates (nondifferential misclassification) or biased estimates (systematic misclassification).

LATE MORTALITY

Five-year survival is often considered a major time for evaluating cancer outcomes, yet 5-year survivors remain at risk for cancer-related death, whether from disease recurrence/progression or sequelae of treatment. Limited information exists on late mortality among pediatric cancer patients treated prior to 1970, when treatment regimens were more likely to include surgical resection with or without radiotherapy, with less exposure to multi-agent chemotherapy. These early reports documented (1) higher death rates in survivors compared to siblings, (2) attribution of death primarily to recurrence of primary malignancy, (3) an increasing risk of non-primary malignancy-related death with increasing time from diagnosis, and (4) associations of treatment modalities and risk of late death (25–27). Selected primary diagnoses were associated with higher rates of late death. For example, prior to CNS-directed radio-therapy for childhood ALL, CNS relapse ultimately led to an

increase in late mortality rates, resulting in 10-year survival probabilities of less than 50%. For Hodgkin lymphoma, Wilms tumor, low-stage neuroblastoma and retinoblastoma that responded well to surgery and radiotherapy, long-term survival rates were substantially higher (13,25).

In the most recently published update of late mortality among the CCSS cohort, 13.8% ($n = 2821$) died after achieving 5-year survival. The estimated probability of survival at 30 years from diagnosis was 81.9% [95% confidence interval (CI) of 81.1–82.7%] (28). The most common reason for late mortality was recurrence or progression of the primary malignancy. However, with increasing time from diagnosis, death due to recurrence/progression has markedly declined while mortality rates for deaths attributable to second neoplasms, cardiac and pulmonary causes have increased (30). By 20 years from diagnosis, the mortality rate due to second malignancy was greater than all other causes of death combined (29).

Radiation therapy is significantly associated with an increased risk for late mortality. Multivariable regression models, controlling for sex, age at diagnosis, time since diagnosis and chemotherapy, but not primary diagnosis or stage, identified that patients who received any radiation exposure had an increased risk [relative risk (RR) 2.9, 95% confidence interval (CI) 2.1–4.2] for death compared to the unexposed population. Survivors who received radiation therapy to the chest or spine or received total-body irradiation (TBI) had a threefold increased risk of cardiac death (RR = 3.3, 95% CI 2.0–5.5) and participants receiving chest or TBI had an elevated but not statistically significant risk for pulmonary death (RR = 1.4, 95% CI 0.7–2.9) (29).

Beyond CCSS, additional insights into late mortality have come from institutional and population-based studies (29–32). While some of these investigations are limited in size and/or ability to fully characterize treatment exposure (e.g., field and dose of radiation), they add to the overall picture of the impact of therapy on risk of late mortality. These observations have translated into reduction or elimination of radiation therapy for specific pediatric cancer populations. Long-term follow-up of cohort like CCSS will provide the evidence base to determine the extent to which reductions in treatment exposure, including radiation therapy, will result in reduced treatment-related late mortality. A recent analysis of a population-based sample of childhood cancer patients suggests that reduction in therapeutic exposures may be resulting in decreased late mortality (33).

SUBSEQUENT NEOPLASMS

The carcinogenic property of radiation is well known. Previous studies of exposed pediatric populations for treatment of Tinea capitis (34) or hemangiomas of the skin (35) or through atomic bomb explosions (36) have documented a linear dose response with exposure and risk and increased risk with younger age at exposure. Subsequent malignant neoplasms have long been recognized as late sequelae of both radiation therapy and chemotherapy for cancer treatment (17,37).

CCSS reported the experience of 13,581 childhood cancer survivors, of whom 298 developed 314 pathologically confirmed subsequent malignant neoplasms. The estimated cumulative incidence of all subsequent malignant neoplasms in the cohort was 3.2% at 20 years after the primary diagnosis of childhood cancer (38). The standardized incidence ratio (SIR) of observed to expected subsequent malignant neoplasms was 6.38 (95% CI 5.69–7.13). The highest rates were observed for new breast cancers (SIR = 16.18; 95% CI 12.35–20.83), bone cancers (SIR = 19.14; 95% CI 12.72–27.67) and thyroid cancers (SIR = 11.34; 95% CI 8.20–15.27) (38). Development of malignancy has long been recognized as a late effect of radiation exposure as part of treatment for childhood cancer (26,39–41). However, while increased risk has been documented, there are rare instances where tissue-specific

dose–response relationships have been determined. One of the major contributions of CCSS has been investigation of dose–response relationships between radiation therapy and risk of a second malignant neoplasm.

Using a nested case-control design, CCSS investigators individually matched (by age, sex and time since original cancer diagnosis) 116 survivors with a subsequent central nervous system (CNS) neoplasm with control subjects (1:4 ratio) consisting of survivors without a subsequent CNS neoplasm (42). Radiation therapy was associated with an increased risk for any subsequent CNS malignant neoplasm, and specifically for subsequent gliomas [$n = 40$, odds ratio (OR) = 6.78, 95% CI 1.54–29.7] and meningiomas ($n = 76$, OR = 9.94, 95% CI 2.17–45.6). Importantly, linear dose–response relationships between radiation dose and the development of both gliomas and meningiomas were identified and were statistically significant. The excess relative risk per Gy, equal to the dose of the linear response function, was 0.33 (95% CI 0.07–1.71) per Gy for gliomas and 1.06 (95% CI 0.21–8.15) per Gy for meningiomas (Fig. 1). After adjustment for radiation dose, there were no statistically significant associations between chemotherapy exposure and the development of a second malignant neoplasm. With increasing length of follow-up, the number of new glioma cases in this population markedly declined (beyond 15–20 years after exposure), which is in contrast to the experience with Tinea capitis and atomic bomb survivors. However, the incidence of meningioma continued to increase with longer length of follow-up.

Previous investigations of survivors of atomic bombs and other analyses of pooled populations have suggested a linear dose response for the development of thyroid cancer after radiation exposure, with a loss of the linear relationship at higher doses of radiation therapy (43,44). In addition, two previous studies among survivors of childhood cancer have suggested a linear dose response with a deviation from the linear model at higher doses (45,46), but no study to date has had a sufficient number of thyroid cancer diagnoses, with a sufficiently wide range of radiation exposures, to comprehensively evaluate the shape of the dose–response curve. Again, using a nested case-control design, CCSS investigators evaluated 69 cases of pathologically confirmed thyroid cancer (47,48). Cases were matched to controls (ratio 1:4) on sex, age at diagnosis of primary cancer, and follow-up interval. Risk of thyroid cancer increased with radiation dose to the thyroid gland for doses up to 29 Gy and decreased for doses greater than 30 Gy (Fig. 1). This linear exponential dose–response model for relative risk was accentuated among patients younger than 10 at the time of exposure who demonstrated a more pronounced increased and decreased risk below and above 30 Gy, respectively. Chemotherapy was not associated with thyroid cancer risk and did not modify the effect of radiation therapy. This finding of increased risk at lower doses and declining risk at higher doses adds supportive evidence consistent with the cell killing hypothesis first proposed in 1965 (49).

Female survivors of childhood cancer are also at risk for secondary breast cancer. In the original CCSS report among 6,068 eligible women, 95 women had 111 confirmed cases of breast cancer. The SIR of developing breast cancer after chest radiation therapy was 24.7 (95% CI 19.3–31.0) compared to an SIR of 4.8 (95% CI 2.9–7.4) for women who received no chest radiation therapy (50). Notably, patients who received ovarian radiation had reduced rates of breast cancer (RR 0.6, 95% CI 0.4–1.0). Patients with a family history of breast cancer (RR 2.7, 95% CI 1.3–2.5) or with a personal history of thyroid disease (RR 1.8, 95% CI 1.1–2.9) had higher risk for developing breast cancer. In Hodgkin lymphoma survivors who received chest radiation, the cumulative incidence of breast cancer at 40 years of age was 12.9% (95% CI 9.9–16.5), and it continued to increase dramatically over the subsequent decade. For survivors without previous chest irradiation, cumulative incidence of breast cancer is highest in sarcoma survivors, reaching 3.3% (95% CI 1.2–5.4) at 40 years of age.

To evaluate the dose–response relationship between chest radiation therapy and the development of breast cancer, 120 confirmed breast cancer cases were identified and matched to controls based on age at initial cancer and time since primary cancer diagnosis (51). A linear relationship was identified between risk of developing breast cancer and radiation dose. At a dose of 40 Gy to the breast, there was an elevenfold increased risk for the development of breast cancer (Fig. 2). The slope of the dose–response curve changed dramatically when the radiation dose to the ovaries was considered because ovarian radiation exposure of 5 Gy or more was associated with a decreased risk of developing breast cancer. These studies represent the largest evaluation to date of breast cancer incidence after treatment for childhood cancer and are similar to those reported by Travis *et al.* in survivors of adult Hodgkin lymphoma (52).

OBESITY AFTER CRANIAL RADIATION THERAPY

Obesity in childhood and adolescence is an important predictor of future risk for adult onset diabetes mellitus, hypertension, dyslipidemia and cardiovascular disease. Even modest weight gain beyond the age of 20 years is strongly associated with increased risk of coronary heart disease. More recently, obesity has been identified as a potential late effect of therapy in survivors of childhood ALL. The underlying pathophysiology of radiation exposure to the hypothalamic-pituitary axis remains unclear. Numerous studies have identified increased weight gain during therapy and early follow-up periods after completion of therapy. However, several of these studies showed no difference in the prevalence of obesity at the attainment of final height among survivors exposure to high doses of cranial radiation compared to lower doses or chemotherapy alone. (53–56). A single study found that patients who received lower doses of cranial radiation were at higher risk (57).

Body mass index (BMI) was evaluated in 1,765 adult survivors of childhood ALL and compared to 2,565 adult siblings of the CCSS cohort. Higher doses of cranial radiation (20–24 Gy) were associated with an increased risk of obesity (BMI ≥ 30.0) in survivors compared to siblings, while no association was identified among survivors who received <20 Gy cranial radiation (58). The age and race adjusted OR for obesity in survivors treated with cranial radiation dose greater than 20 Gy in comparison with siblings was 2.59 for females (95% CI 1.88–3.55) and 1.86 for males (95% CI 1.33–2.57). Follow-up of this population of survivors at a mean interval of 7.8 years identified changes in BMI from baseline enrollment (59). While the mean BMI of both siblings and survivors increased with age, female ALL survivors who were treated with cranial radiation had a significantly greater increase in BMI (women, 0.41 units/year, 95% CI, 0.37–0.45 units; Fig. 3). Importantly, females treated with doses of cranial radiation (10–19 Gy) who at baseline had a BMI not significantly different from CCSS female siblings, at 10-year follow-up demonstrated a BMI similar to those treated with >20 Gy of radiation therapy. Chemotherapy was not associated with an increase in BMI; however, younger age at radiation exposure was a significant modifying factor. While mechanisms for an increased rate of obesity among women after cranial irradiation are not well understood, there are other instances where female survivors exposed to radiation therapy demonstrate a higher occurrence of late effects (e.g., neurocognitive outcomes, earlier onset of puberty, and reduced final height) (60). Additionally, among the ALL female survivors in the CCSS, the polymorphism in the leptin receptor gene, Gln223Arg, demonstrated a statistically significant interaction between genotype (homozygous for the arginine allele) and radiation exposure, with a sixfold greater odds of having a BMI ≥ 25 (95% CI 2.1–22.0) (61).

PULMONARY AND CARDIAC COMPLICATIONS

Since the lung is a radiosensitive organ, understanding long-term effects of pulmonary irradiation is essential. Long-term pulmonary toxicity is characterized by pulmonary fibrosis, which is typically asymptomatic in its earliest phases yet eventually may cause dyspnea and nonproductive cough. Early studies of survivors of Wilms tumor have suggested that pulmonary radiation therapy at an early age led to significant reductions in lung volumes and dynamic compliance over time as well as decreased chest wall growth (18,19). In addition, known associations between chemotherapy (including bleomycin, busulfan and cyclophosphamide) and pulmonary fibrosis have been well documented (62,63).

Within the CCSS cohort, radiation exposure (defined as exposure to the chest or total-body radiation, as a dichotomous variable, yes/no) was associated with a cumulative incidence of lung fibrosis at 20 years of 3.5% (64). Chest radiation therapy was statistically significantly associated with lung fibrosis (RR = 4.3; $P = 0.001$), supplemental oxygen use (RR = 1.8; $P < 0.001$), recurrent pneumonia (RR = 2.2; $P = 0.001$), and chronic cough (RR = 2.0; $P < 0.001$) (Fig. 4). Associations for specific pulmonary outcomes were also identified with specific chemotherapy agents including cyclophosphamide, bleomycin, busulfan, carmustine (BCNU) and lomustine (CCNU). Unfortunately the cumulative incidence of lung fibrosis, chronic cough and shortness of breath with exercise continues to increase up to 25 years from the time of diagnosis (Fig. 4) for individuals who received radiation to the chest, a finding that warrants further follow-up as these patients age into adulthood. These data quantify risk for adverse pulmonary outcomes over an extended period of follow-up. It is striking that the cumulative incidence continues to increase long after the initial exposure.

Cardiac toxicity among childhood cancer survivors reflects a major cause of morbidity and mortality. Both chemotherapy (i.e. anthracyclines) and radiation are known to be cardiotoxic (65). Radiation exposure to the heart has been associated with heart failure, pericardial injury, myocardial fibrosis, dysrhythmias, valvular abnormalities and premature coronary artery disease (66). Assessment of the CCSS cohort demonstrated that cardiac radiation therapy of 15 Gy or more increased the risk of congestive heart failure, myocardial infarction, pericardial disease and valvular abnormalities by two- to sixfold compared to nonexposed survivors (67).

ABNORMALITIES IN THYROID FUNCTION

Hypothyroidism is the most commonly reported abnormality of the thyroid gland after radiation exposure, but hyperthyroidism and development of thyroid nodules occur as well (15,16,68). The greatest risk for hypothyroidism occurs in the first 5 years, but late onset of hypothyroidism can occur beyond 20 years after exposure (15). The incidence of hyperthyroidism has been reported for several adult populations treated with neck irradiation, and the reports describe a clinical picture consistent with Graves' disease, with a diffusely enlarged thyroid gland, elevated levels of thyroid hormone, decreased thyroid stimulating hormone, and development of autoantibodies to the thyroid (15,69,70). The incidence of thyroid nodules has previously been reported to range from 2–65% depending on length of follow-up and method of detection (15,16,71–74).

In an evaluation of 1,791 Hodgkin lymphoma survivors in the CCSS cohort, 34% reported at least one thyroid abnormality (75). Hypothyroidism was most commonly reported (RR = 17.1; $P < 0.001$ compared to the sibling population). Female sex, older age at the time of diagnosis, and higher radiation doses (Fig. 5) were all independently associated with an increased risk of hypothyroidism. For patients who received more than 45 Gy for treatment of their Hodgkin lymphoma, the actuarial risk of hypothyroidism was 50% at 20 years from

diagnosis. Hyperthyroidism was reported by only 5% of survivors, but this incidence was eightfold greater than that reported by siblings. The risk of thyroid nodules was 27 times ($P < 0.0001$) that of sibling controls, and the actuarial risk of thyroid nodules was 20 % at 20 years from diagnosis.

While the association between hypothyroidism and higher radiation doses has been well established, the report by CCSS clarifies the long-term incidence of this entity and underscores the need for extended clinical surveillance.

CHRONIC HEALTH CONDITIONS

While great strides have been made in documenting the incidence/prevalence of specific health-related outcomes among long-term survivors, it has been more challenging to present a comprehensive picture of overall health conditions and associated treatment exposures. Previous studies have been limited by both sample size and detail of specific exposures (76–79). Moreover, none of these previous studies used a control population to permit comparison to a referent sample and to quantify risk. Last, it is important to note that these outcomes were reported among survivors who were still relatively young and thus do not provide information regarding health conditions within a framework of aging.

The large size of the CCSS cohort and the comprehensive nature of the self-report evaluation has allowed for detailed reporting and estimation of the overall prevalence of chronic medical conditions. Using the Common Terminology Criteria for Adverse Events (version 3) scoring system developed by the National Cancer Institute, investigators scored long-term medical conditions and calculated the frequency of chronic conditions in over 10,397 survivors and 3,034 siblings within the CCSS cohort (80). At a mean age of 26.6 years, 62.3% of the survivor population had at least one chronic medical condition and 27.5% had a severe or life-threatening medical condition compared to 36.8% and 5.2%, respectively, for siblings. The risk of developing any chronic condition in the survivor was 3.3 (95% CI 3.0–3.5) compared to siblings and 8.2 (95% CI 6.9–9.7) for severe or life-threatening conditions. The independent effect of radiation therapy on development of a chronic medical condition was significant. Exposure to radiation therapy significantly increased the risk of developing any medical condition (RR = 3.4; 95% CI 3.1–3.6). Radiation therapy was associated with an eightfold increase of having a severe or life-threatening medical condition (RR = 7.9; 95% CI 6.6–9.4). Patients who received radiation therapy to the brain, chest, abdomen or pelvis demonstrated increased risk for long-term medical conditions (Fig. 6) (80). Multiple associations with chemotherapy were identified; however, five treatment combinations were determined to increase the risk for a severe or life-threatening condition at least 10-fold. Four of these combinations included radiation therapy to the brain, pelvis or abdomen, identifying these populations as high-risk for future complications and in need of comprehensive long-term follow-up.

CONCLUSION

In summary, improvements in primary therapy now lead to almost 80% of children diagnosed with cancer surviving 5 years from their primary malignancy. Therefore, importance must be placed on defining the incidence of long-term effects of cancer therapy and the impact of these effects on the survivors. Radiation therapy is essential for many primary cancers. The CCSS cohort, consisting of 5-year survivors diagnosed between 1970–1986, has provided important new information relating to radiation therapy and long-term morbidity and mortality. The heterogeneity of radiation dose within the unique resource of the CCSS allows for further refinement of the associations between radiation therapy and long-term outcomes. More specifically, dose–response associations have been described for

subsequent malignant neoplasms. These findings go beyond confirmation of previous associations identified in studies with smaller populations to quantify dose-specific long-term risks. In addition, these findings in regard to dose response with radiation therapy and latent period after radiation therapy are similar to earlier findings for atomic bomb survivors.

It is essential moving forward to limit both the dose and the extent of the field for radiation therapy in an attempt to reduce the risk of these long-term outcomes. The current CCSS cohort diagnosed and treated between 1970–1986 represents an era prior to conformal radiation technique. Thus findings from this cohort may not be applicable to children being treated today. Current modalities such as conformal radiation therapy, intensity-modulated radiation therapy (IMRT), and proton-beam therapy may allow the focus of radiation upon the target tissue with reduction of dose to surrounding parenchyma. Future studies should therefore focus on temporal changes in patterns of late effects based on modifications in the delivery of radiation. Current expansion of the CCSS cohort to include patients diagnosed between 1987–1999 will facilitate crucial evaluations of conformal techniques.

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FIG. 1.

Relative risk with 95% confidence intervals of subsequent glioma, meningioma (open boxes, mean observed relative risk for meningioma; closed boxes, mean observed relative risk for glioma; solid line, fitted line for meningioma risk; hatched line, fitted line for glioma risk), and thyroid neoplasms (solid line represents linear dose–response model for relative risk, hatched line represents linear exponential dose–response model for relative risk) within the Childhood Cancer Survivor Study by radiation dose. Reprinted with permission from *J. Natl. Cancer Inst.* **98**, 1528–1537 (2006) and from *Lancet* **356**, 2014–2023 (2005).

FIG. 2.
Fitted breast cancer risk by radiation dose to the breast and ovary. Reprinted with permission from *J. Clin. Oncol.* **27**, 3901–3901 (2009).

FIG. 3. Model-based estimates of linear changes in mean body mass index (BMI) at baseline and follow-up for 706 survivors of acute lymphoblastic leukemia treated with >20 Gy cranial radiation compared to siblings. Reprinted with permission from *J. Clin. Oncol.* **26**, 4639–4645 (2008).

FIG. 4.

Cumulative incidence of lung fibrosis, chronic cough, and exercise induced shortness of breath in the CCSS cohort with increasing time from diagnosis based on exposure to chest radiation (XRT), pulmonary-toxic chemotherapy, both or neither. Reprinted with permission from *Cancer* **95**, 2431–2441 (2002).

FIG. 5. Probability of developing an underactive thyroid after diagnosis of Hodgkin lymphoma according to dose of thyroid radiation (RT).

FIG. 6. Relative risk with 95% confidence intervals of developing a chronic medical condition (grade 1–4, grade 3 or 4, ≥ 2 conditions) based on radiation exposure (RT) compared to siblings.