VOLUME 27 · NUMBER 14 · MAY 10 2009

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Chronic Disease in the Childhood Cancer Survivor Study Cohort: A Review of Published Findings

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Submitted December 4, 2008; accepted March 3, 2009; published online ahead of print at www.jco.org on April 13, 2009.

Supported by Grant No. U24-CA55727 from the National Cancer Institute (L.L.R., principal investigator) and by support to St Jude Children's Research Hospital from American Lebanese Syrian Associated Charities.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2714-2339/$20.00

DOI: 10.1200/JCO.2008.21.1953

INTRODUCTION

A primary objective of the Childhood Cancer Survivor Study (CCSS) is to characterize the major chronic health conditions faced by childhood cancer survivors, and to determine the risk factors for those conditions. In order to characterize these conditions, at entry into the study, participants completed questionnaires that documented self-reported chronic illnesses, symptoms, and medications. Over time, follow-up questionnaires (administered approximately every 2 to 3 years) have allowed analysis of changes in symptoms and disease burden. To date, analyses have been completed which describe the profile of chronic disease in the cohort at first entry into the study and for specific subgroups, defined by primary cancer, by specific exposures, and by demographic factors.[1,2] Generally, these analyses estimate risk of chronic disease by calculating a risk estimate for self-reported symptoms or conditions. Relative risks for chronic disease or specific conditions are calculated comparing the survivor cohort with the sibling cohort or population norms. In addition, relative risk for an outcome in a subgroup with a specific treatment exposure or demographic characteristic is calculated relative to a comparison group without that specific factor of interest. Cumulative incidence of specific chronic illnesses is estimated in many of the reports, and analyses of chronic illnesses in each of the survivor groups by primary diagnosis are completed (acute lymphoblastic leukemia [ALL],[3] acute myeloid leukemia [AML],[4] and rhadbdomyosarcoma[5]) or in progress (neuroblastoma, bone sarcoma, renal tumors, lymphomas, and brain tumors).

This review presents the completed analyses of overall chronic illness in the original cohort and then describes findings by organ system. Specific chronic diseases reported here will include: endocrinologic disorders (including thyroid disease, disorders of growth, weight, and pubertal regulation), osteonecrosis, cardiac disease, pulmonary conditions, and neurosensory/neurologic adverse outcomes. Adverse outcomes in some domains which might be considered chronic illnesses—secondary cancers, emotional and psychological disorders, pain—are not covered herein, but are reviewed separately in other articles within this issue of *Journal of Clinical Oncology*. For some outcomes, only subsets of the cohort have been analyzed, often because a hypothesis regarding a specific exposure or disease (eg, weight regulation in leukemia survivors or stroke after neck radiation therapy [RT]) has been explored. Analyses in progress, and not included in this report, include risk of renal and urinary disorders, gastrointestinal diseases, and more in depth cohort-wide characterizations of cardiovascular disease. Additional studies to characterize further longitudinal changes in risk as the cohort ages are planned.

CHRONIC ILLNESS OVERALL

Chronic diseases in long-term childhood cancer survivors can involve multiple organ systems and have a wide spectrum of severity. One way to capture the burden of morbidity in survivors is to ask for a self-assessment of overall general health and then compare the grouped responses with that of grouped sibling responses. Self-assessment of overall health was ascertained as part of the baseline questionnaire (complete baseline questionnaire is available at www.stjude.org/ccss). Hudson et al analyzed the health status of 9,535 adult survivors ($\geq$ 18 years of age) in the cohort, using 2,916 randomly selected siblings from the families of the cancer survivors as a comparison group.[1] Survivors and siblings in the two cohorts were asked at baseline "Would you say that your health is excellent, very good, good, fair or poor?" Self-reported fair or poor health was observed in 10.9% of survivors compared with 4.9% of siblings. Specific demographic factors associated with this self-report of reduced general health included female sex, lower income and educational attainment, and older age at interview. Cancer-related risk factors for self-reported poor health included a primary diagnosis of bone tumor, CNS tumor, and Hodgkin's disease (HD).[1]

Understanding the contributing factors to this self-described detriment in health was the goal of further analyses.

To systematically analyze the prevalence and severity of the self-reported chronic medical conditions reported by cohort members, Oeffinger et al adapted a well-accepted toxicity scoring system utilized most frequently for new drug evaluations in cancer clinical trials (the National Cancer Institute's Common Toxicity Criteria for Adverse Events [CTCAE] version 3.0).[6] Questionnaire-based data from the baseline questionnaire were mapped to organ-specific toxicities listed in the CTCAE using a 5-point severity scale from mild (severity score = 1) to life-threatening or disabling (score = 4) or fatal (score = 5). In a landmark publication, Oeffinger et al reported on the prevalence, incidence, and severity of chronic disease (self-reported), analyzing 137 specific conditions in the 10,397 cohort members who were older than 18 years of age at entry into the CCSS study and compared them with a similar-aged sibling cohort enrolled in CCSS. At the time of the analysis, the mean age of both the survivor and sibling cohorts was 26.5 years with a range of 18 years to 56 years, and the interval from time of primary diagnosis of cancer to time of interview was 17.5 years with a range of 6 to 31 years. Approximately two thirds (67.4%) of the survivors were known to have had a prior exposure to RT and 62% had been exposed to chemotherapy as treatment for their primary cancer.[7]

Oeffinger et al[7] reported that childhood cancer survivors have a high risk of development of significant chronic conditions, and that many members of the cohort suffer from more than one chronic illness. The authors reported that the prevalence of at least one severe (grade 3), or life-threatening/disabling (grade 4) chronic illness was 27.5% among survivors, compared to 5.2% in siblings. In addition, the prevalence of multiple conditions was high, with 23.8% of survivors reporting more than three conditions (compared with 5.4% of siblings).

Severe or life-threatening conditions in the survivor cohort and their associated relative risk compared to the sibling comparison group included: congestive heart failure (relative risk [RR], 15.1; 95% CI, 4.8 to 47.9); coronary artery disease (RR, 10.4; 95% CI, 4.1 to 25.9); cerebrovascular accident (RR, 9.3; 95% CI, 4.1 to 21.1); and renal failure or dialysis (RR, 8.9; 95% CI, 2.2 to 36.6). Although the percentage of survivors reporting any one of the above conditions was low (fewer than 2% of the overall cohort for each), the relative risks were substantial. Perhaps even more striking was the cumulative incidence of chronic conditions noted in the report. Overall, the cumulative incidence of a grade 3, 4, or 5 chronic condition in the cohort was 33.1% at 25 years after primary diagnosis. Of note, this published analysis included the occurrence of secondary malignancy as either a chronic grade 4 or 5 outcome.

In Figure 1, cumulative incidence of organ-system toxicity in the overall CCSS cohort is presented. This analysis utilized the same CCSS data set as Oeffinger et al[7] but excluded secondary malignancy as a chronic disease, given that analyses of secondary cancers in the CCSS are presented in other articles in this issue of *Journal of Clinical Oncology*. Of particular interest is the slope of the cumulative incidence curves for endocrine, pulmonary, and cardiac disease, suggesting that the cohort continues to face new-onset organ system morbidity as the cohort members age and long after treatment concludes. The proportion of survivors and siblings reporting an organ-specific chronic illness, and the associated relative risks are presented in Table 1. The percentage of survivors reporting a severe, disabling, life-threatening, or fatal condition for any one chronic disease group ranges from 0.8% (renal condition) to 7.6% (endocrine condition), and the RRs compared to siblings are striking, with survivors 7.5 (95% CI, 6.4 to 8.9) times more likely to have a grade 3, 4, or 5 condition. It should also be noted that self-report may underestimate some of the chronic conditions that might be expected in this cohort, in particular gastrointestinal, renal, and musculoskeletal toxicity. Follow-up questionnaires, as well as ancillary studies that directly measure these conditions, will further refine these estimates and present a more detailed analysis of survivor health.

Oeffinger et al[7] found that survivors of all primary cancer diagnoses had an increased relative risk of development of grade 3 or 4 chronic conditions when compared with siblings (adjusting for age, sex, and race/ethnic group); the highest RRs were associated with a primary diagnosis of bone tumors (RR, 38.9; 95% CI, 31.2 to 48.5) and CNS tumors (RR, 12.6; 95% CI, 10.3 to 15.5). Survivors exposed to any RT, any chemotherapy, and specific treatment combinations were all found to have significantly elevated RRs of severe or life-threatening conditions compared with siblings. The risk of a grade 3 or 4 chronic condition was at least 10-fold above the risk in siblings for survivors with the following exposures: abdominal or pelvic RT plus an alkylating agent (RR, 10.0; 95% CI, 8.2 to 12.1), an anthracycline plus an alkylating agent (RR, 10.9; 95% CI, 9.0 to 13.1), chest RT plus bleomycin (RR, 13.6; 95% CI, 9.8 to 18.7), chest RT plus an anthracycline (RR, 13.0; 95% CI, 10.4 to 16.3), chest RT plus abdominal or pelvic irradiation (RR, 10.9; 95% CI, 8.9 to 13.2). As shown in Figure 2 (left panel), RT alone, chemotherapy alone, and the combination of chemotherapy and RT are associated with an increasing cumulative incidence of chronic illness over time. Interestingly, the cumulative incidence of chronic grade 3, 4, or 5 conditions for patients treated with RT alone slopes upward at approximately 10 years after diagnosis, confirming the late onset pattern of radiation damage. Note that the incidence rates shown in the figures, and those discussed throughout this article, are left truncated at 5 years after diagnosis, reflecting the eligibility entry criteria for the cohort. Also, as mentioned previously, the data presented in Figure 2 exclude secondary malignancies as a chronic condition.

Finally, Figure 2 (right panel) presents the relative cumulative incidences of chronic conditions in patients treated with different radiation fields. Of note, total body radiation (TBI) results in the highest cumulative incidence of significant chronic illness, despite the relatively low radiation doses associated with this therapy. TBI is highly associated with certain underlying cancer diagnoses and other nonradiation therapies. Multivariate analyses may elucidate further the contribution of specific diagnoses and pre- and post-transplant therapies to this TBI-associated burden of chronic illness.

The availability of cohort studies outside of North America generally confirm the high burden of chronic disease in childhood cancer survivors. In the Netherlands, Geenen and colleagues reported on the health of 1,315 survivors with a median age of 24.4 years at the time of assessment.[8] Their analysis benefited from nearly complete follow-up, with 94.3% of the survivors participating (compared with 81.2%[9] in the CCSS), and outcomes were directly measured in a clinical setting, rather than by self-report. Compared with the CCSS, this cohort is quite homogeneous, both because primary therapy in the Netherlands is quite uniform and in terms of lack of ethnic and racial diversity. Given these differences, it is remarkable to note that the findings are quite similar: in the Dutch cohort, 70% of survivors have at least one

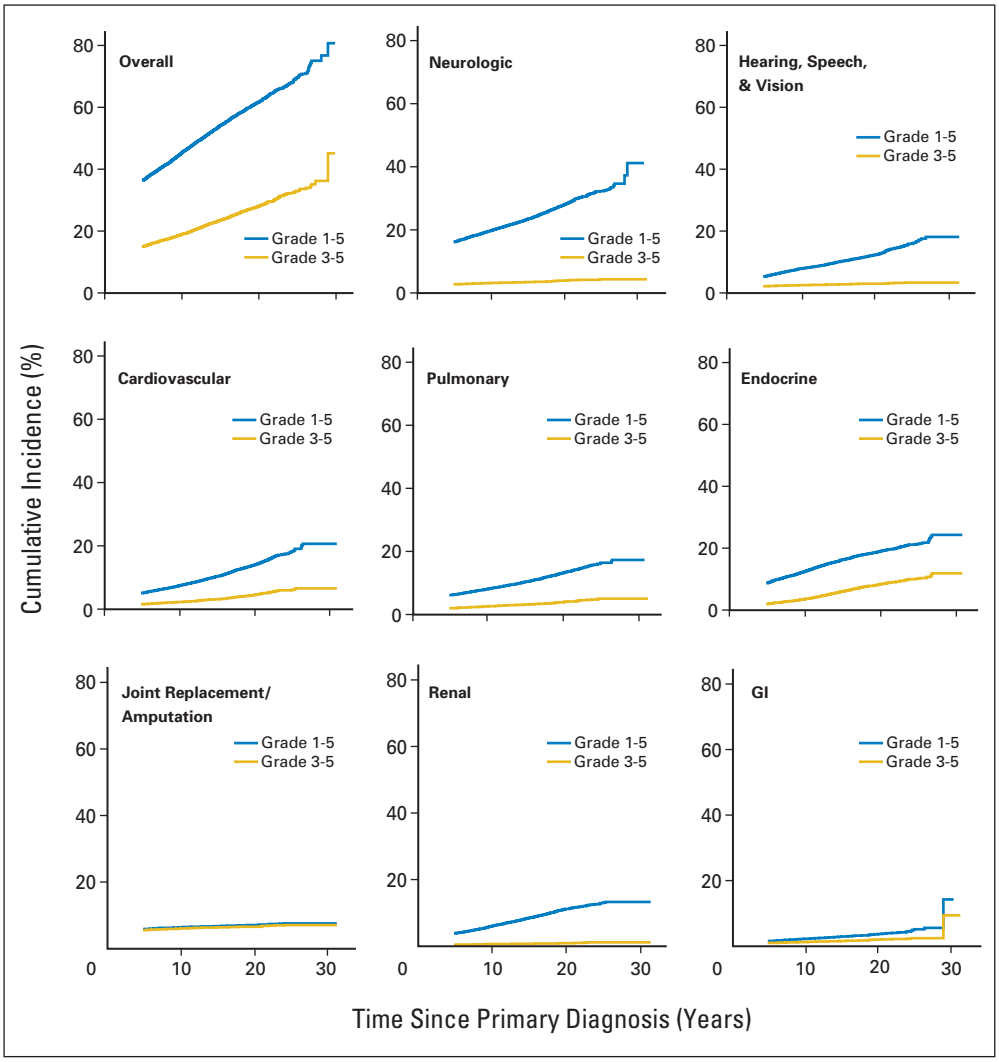

Fig 1. Cumulative incidence of chronic health conditions (grade 1 to 5 and grade 3 to 5).

chronic condition and 40% have at least one severe or disabling condition. The somewhat higher proportion of survivors having significant chronic disease in this report compared to the CCSS may be due to the methods used, including direct measurement of outcome rather than self-report. Similarly, the British Childhood Cancer Survivor Study, another population-based study, has reported its initial findings in a cohort of childhood cancer patients diagnosed in Britain between 1940 and 1991, and known to have survived 5 years. The strength of this cohort includes the large size, long follow-up, and the ability to link to British National Health Service data on participants.[10]

ENDOCRINOLOGIC ILLNESS AND DISORDERS OF GROWTH

Thyroid Disease

Abnormalities of the thyroid gland, including primary hypothyroidism, hyperthyroidism, and thyroid neoplasms all have been reported to occur at a higher rate among survivors of childhood cancer compared with the general population.[11-14] Primary hypothyroidism is the most common thyroid disturbance that occurs in this population. It generally results from direct damage to the thyroid gland after external-beam RT. Thus, primary hypothyroidism can develop in survivors who have been treated with neck/mantle RT for HD, craniospinal RT for brain tumors, and TBI as cytoreduction for stem-cell transplantation.[11-15] Whereas external-beam RT to the thyroid gland has emerged as the major risk factor for the development of a thyroid abnormality, interactions between RT and various patient (eg, age, sex) and treatment variables (eg, chemotherapy) in the genesis of these thyroid problems have been difficult to characterize, owing to the small sample size and homogeneity of treatments in the majority of published studies.

Thyroid disease in survivors of HD. In an attempt to overcome the limitations inherent in most single institution studies, CCSS reported on the spectrum of thyroid abnormalities recorded by 1,791 (959 males) HD survivors enrolled in the study.[15] Thyroid abnormalities were ascertained as part of the baseline questionnaire. Survivors were a median age of 14 years (2 to 20 years) at diagnosis of HD and a median age of 30 years (range, 12 to 47 years) at follow-up. Data were compared to 2,808 siblings of participants in the CCSS. Seventy-nine percent of survivors had been treated with RT, with the median dose of radiation to the thyroid of 35 Gy (range, 0.0037 to 55 Gy). Thirty-four

Table 1. Relative Risk of Chronic Health Condition by Major Organ System As Compared With Siblings

Health Condition*	Grade 1-4: Survivors (n = 10,398) No.	%	Siblings (n = 3,083) No.	%	Relative Risk	95% CI	Grade 3 or 4: Survivors (n = 10,398) No.	%	Siblings (n = 3,083) No.	%	Relative Risk	95% CI
None	4,064	39.1	1,950	63.3	NA	NA	†		†		NA	NA
Any chronic	6,325	60.8	1,133	36.7	3.1	2.9 to 3.4	2,779	26.7	167	5.4	7.5	6.4 to 8.9
Cardiac	1,336	12.8	284	9.2	1.9	1.6 to 2.1	406	3.9	22	0.7	7.5	4.8 to 11.7
Endocrine‡	1,886	18.1	137	4.4	5.9	4.9 to 7.1	788	7.6	56	1.8	6	4.5 to 7.9
Neurologic	2,837	27.3	371	12.0	3.3	2.9 to 3.7	314	3.0	13	0.4	9.5	5.2 to 17.4
Disorder of hearing, speech, or vision‡	1,252	12.0	193	6.3	2.5	2.2 to 3.0	317	3.0	21	0.7	5.8	3.6 to 9.4
Pulmonary	1,227	11.8	177	5.7	2.8	2.4 to 3.3	303	2.9	37	1.2	3.1	2.2 to 4.4
Renal	1,045	10.1	263	8.5	1.5	1.3 to 1.8	88	0.8	5	0.2	8.1	2.9 to 23.1
Gastrointestinal‡	410	3.9	43	1.4	3.7	2.6 to 5.1	241	2.3	14	0.5	5.7	3.3 to 9.7
Musculoskeletal‡	772	7.4	11	0.4	35.2	16.7 to 74.1	725	7.0	3	0.1	77.1	24.9 to 238.7

NOTE. Adjusted for race and sex; age used as the timeline.
Abbreviation: NA, not available.
*Subsequent malignant neoplasms are excluded throughout.
†Same as any grade 1-4.
‡No grade 4.

percent of the survivor cohort had been diagnosed with at least one thyroid abnormality.

Hypothyroidism was the most common disturbance, with a RR of 17.1 ($P < .0001$) compared to siblings (Appendix Table A1, online only).[15] It is important to note that this RR is almost certainly an overestimate as it fails to take into account the possibility that survivors were more likely to have been screened for thyroid dysfunction than were the sibling comparison group. Thus, it is possible that more cases of subclinical hypothyroidism were diagnosed among the HD survivors compared with the siblings.

Increasing dose of radiation, older age at diagnosis of HD, and female sex were all independently associated with an increased risk of hypothyroidism.[15] Whereas higher doses of radiation have been found consistently to increase the risk of hypothyroidism,[13,14] the importance of age at diagnosis of HD and sex has been less clear. The greatest risk of hypothyroidism occurred during the first 5 years after treatment, particularly in the group who received ≥ 45 Gy radiation, but new cases continued to emerge more than 20 years after the diagnosis of HD (Fig 3).

Hyperthyroidism was reported by 5% of survivors, which was eight-fold greater ($P < .0001$) than the incidence reported by the sibling comparison group (Appendix Table A1). The development of hyperthyroidism after treatment for HD has been reported by several groups, primarily in adult subjects treated with neck RT.[14,16,17] The absolute risk of developing hyperthyroidism in our pediatric HD survivors (150 to 160 cases per 100,000) was nearly identical to that reported by Hancock et al (170 to 188 cases per 100,000).[14] Thyroid dose ≥ 35 Gy was the only risk factor we could identify for hyperthyroidism, similar to what has been observed in adults treated for HD.[14]

The risk of an HD survivor being diagnosed with a thyroid nodule was 27 times ($P < .0001$) that of sibling controls (Appendix

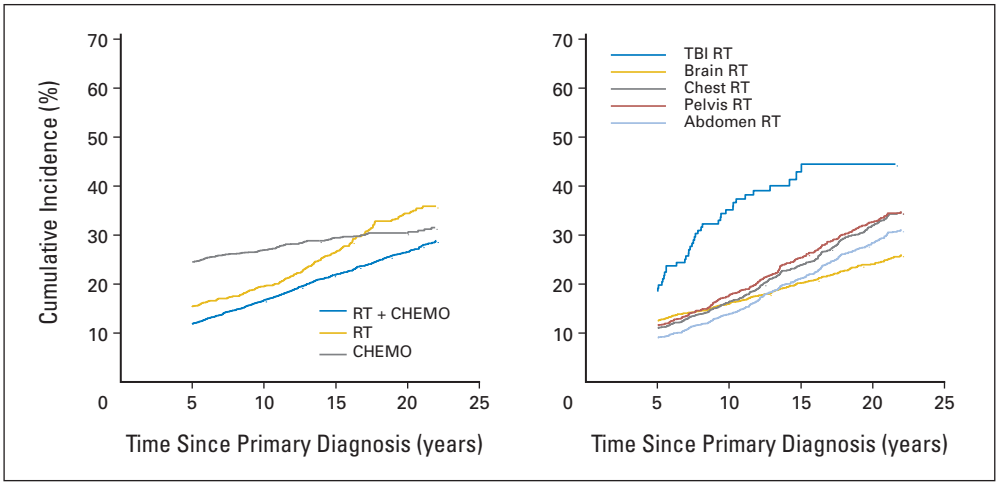

Fig 2. Cumulative incidence of chronic health conditions by exposure (grade 3 to 5 only). Survivors exposed to radiation in more than one anatomic site are included in each appropriate radiation curve in the right panel. RT, radiation therapy; CHEMO, chemotherapy; TBI, total body irradiation.

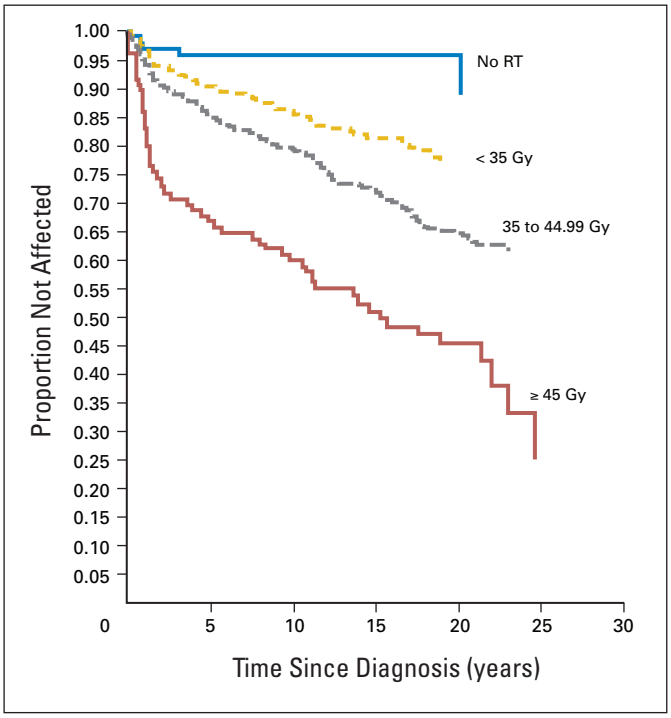

Fig 3. Probability of developing an underactive thyroid after diagnosis of Hodgkin's lymphoma. RT, radiation therapy.

Table A1).[15] The reported incidence of thyroid nodules among HD survivors has varied greatly depending on the length of follow-up and the methods employed (ie, palpation *v* ultrasound) to examine the thyroid.[14,18,19] Female sex and radiation dose to the thyroid ≥ 25 Gy were independent risk factors for thyroid nodules in this CCSS study. The actuarial risk of a female survivor developing a thyroid nodule was 20% at 20 years from diagnosis.

Among the 146 cases of thyroid nodules, 11 (7.5%) were found to have thyroid cancer. In addition, there were nine cases of thyroid cancer among the survivors who did not report having had thyroid nodules. Thus, there were a total of 20 cases of thyroid cancer among the HD survivors (Appendix Table A2, online only).[15] The standardized incidence ratio of thyroid cancer in the HD survivors was 18.3 compared to the general population, based on Surveillance, Epidemiology, and End Results data. A wide range of RR estimates for thyroid cancer (range, 9.7 to 67) have been reported in pediatric HD survivors.[14,20-23] In the CCSS study, all thyroid cancers were well differentiated and the majority was papillary carcinoma, as has been reported consistently by others. The latency period for the development of thyroid cancer varied from 5 to 26 years.

Considering that the HD survivors had an exposure that is known to result in thyroid neoplasms (ie, RT to the neck), it is likely that they have been subjected to more consistent and frequent medical surveillance (eg, thyroid palpation and ultrasound) than the sibling comparison group. Thus, the RR estimates for thyroid nodules and thyroid cancer derived from this study are likely to be overestimated because the sibling group will represent an underestimated rate of subclinical disease.

Our data indicate that young adult HD survivors who were treated with RT to the thyroid gland are at substantially increased risk for the development of a spectrum of abnormalities of the thyroid. Female survivors are at particularly high risk of developing hypothyroidism and thyroid nodules. Periodic testing of thyroid function along with regular surveillance for the development of thyroid neoplasms should be performed throughout the entire life span of pediatric HD survivors.

Thyroid disease in survivors of brain tumors. Endocrine outcomes were assessed in 1,607 survivors of childhood brain tumors (CBT) who were enrolled in the CCSS, based on their responses to the baseline questionnaire.[24] For comparison, data were also collected from 3,418 randomly selected siblings of participants in the CCSS. Hypothyroidism (including both primary and central hypothyroidism) was reported in 16% of CBT survivors. The RR of a CBT survivor developing hypothyroidism 5 or more years after diagnosis of a brain tumor was 14.3 (95% CI, 9.7 to 21.0; $P < .001$) compared with a sibling.[24] The risk of hypothyroidism in cases who received a radiation dose of ≥ 25 Gy to the thyroid was more than twice that of CBT survivors who received less than 25 Gy to the thyroid (RR, 2.7; $P < .0001$). These results are in keeping with previous data on hypothyroidism in survivors of CBT[12,25] and indicate that survivors who receive high-dose craniospinal RT (ie, survivors of medulloblastoma/primitive neuroectodermal tumor) are at significant risk of developing primary hypothyroidism over time. Lifelong screening of thyroid function is warranted in this group. Hyperthyroidism (n = 20) and thyroid nodules (n = 17) occurred too infrequently to allow for meaningful statistical analysis.[24]

Thyroid disease in survivors of rhabdomyosarcoma. Among 606 survivors of rhabdomyosarcoma enrolled in the CCSS, self-reported hypothyroidism (both primary and central) was reported by 9% of survivors compared to 1% of siblings.[5] Survivors of head and neck tumors accounted for more than 75% of cases with hypothyroidism. The RR of hypothyroidism more than 5 years from diagnoses was 6.9 (95% CI, 4.1 to 11.3) in survivors compared to siblings. Exposure to head or neck RT was the major risk factor for hypothyroidism.

Disorders of Growth and Growth Hormone Therapy

The determinants of final height in cancer survivors are multifactorial and include both hormonal (eg, growth hormone deficiency, precocious puberty) and nonhormonal factors (eg, RT injury to the growth plates or spine, nutritional status, midparental height). Growth hormone deficiency secondary to radiation-induced hypothalamic-pituitary injury is thought to be one of the mechanisms by which decreased height occurs.[26] Precocious puberty, or even more subtle changes in pubertal timing, also may contribute to adult short stature after cranial RT, particularly in girls.[26,27] The availability of treatment information in a large number of survivors in the CCSS allows analysis of the role of some of these multiple factors and their influence on growth and final adult height.

Adult Height

Brain tumor survivors. Height attainment and risk of adult short stature was examined among brain tumor survivors enrolled in CCSS, with 13% of survivors having adult heights two or more standard deviations below population norms.[24] While the final heights of brain tumor survivors who were not treated with RT were only minimally different from population norms, survivors exposed to cranial or craniospinal RT, particularly those diagnosed at younger than 10 years of age, were at significantly increased risk of short stature compared with nonirradiated survivors (Fig 4, upper panel). A dose-dependent

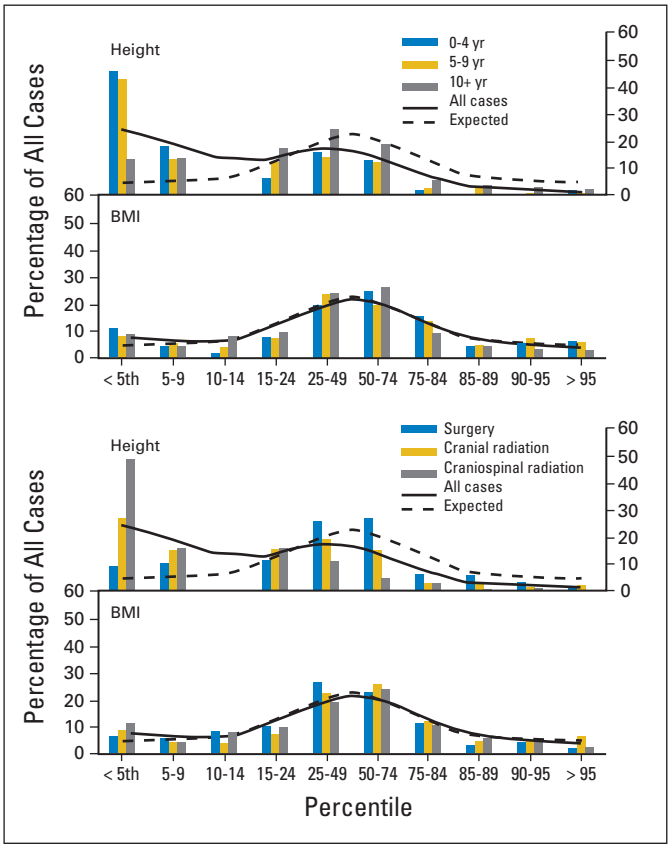

Fig 4. Age- and sex-specific percentiles for height and body mass index (BMI) among brain cancer survivors by age at diagnosis (upper panel) and treatment types (lower panel).

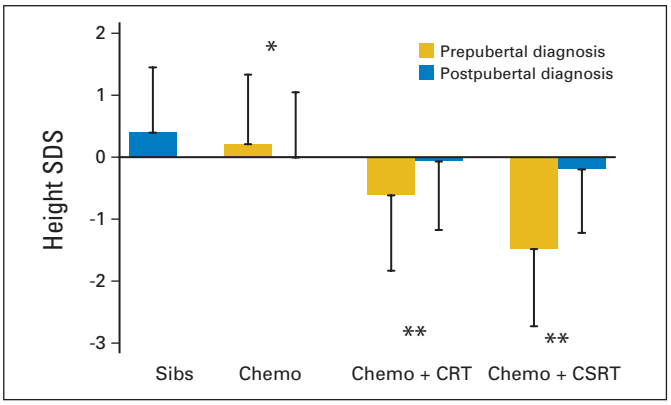

Fig 5. Height standard deviation scores (SDS) across exposure groups by pubertal status at acute lymphoblastic leukemia diagnosis. Box height represents mean height SDS in the group. (*) $P < .05$; (**) $P < .001$ by t-test for differences. Sibs, siblings; Chemo, chemotherapy, CRT, cranial radiotherapy; CSRT, craniospinal radiotherapy.

effect of RT to the hypothalamic-pituitary axis (HPA) on adult stature was observed, with doses from 20 to 59 Gy associated with a three-fold increased risk of adult height in the lower 10th percentile (adult short stature), whereas doses ≥ 60 Gy were associated with nearly a six-fold increased risk of adult short stature. Spinal RT was not found to be an independent risk factor among brain tumor survivors once the data were adjusted for RT dose to the HPA. However, other studies have generally found spinal RT to be associated with subsequent shorter stature.[28,29]

ALL survivors. Nine percent of ALL survivors who are participants in the CCSS also reported having adult heights more than two standard deviations below population norms.[29] Survivors treated with cranial RT received doses primarily between 15 and 29 Gy, and similar to the brain tumor analysis discussed in the previous paragraph, a dose-dependent effect was seen. With nonirradiated same age survivors as the referent group, prepubertal children treated with ≥ 20 Gy cranial RT had a near eight-fold increased risk of adult short stature compared with a four-fold risk among those treated with less than 20 Gy. Exposure to spinal RT was associated with further height decrement among prepubertal ALL survivors. CNS RT exposure was not associated with significant short stature among children diagnosed at older ages (Fig 5). Independent of age at diagnosis, ALL survivors treated with chemotherapy alone also had a three-fold risk of short stature versus comparison siblings, although no specific chemotherapy agent or treatment intensity level was associated with reduced final height. Findings from two earlier studies that examined longitudinal growth in ALL survivors treated without RT suggest that height loss occurred primarily during active therapy without adequate catch-up growth subsequently.[30,31]

Treatment With Growth Hormone

Growth hormone deficiency (GHD) is among the most common endocrinopathies noted in survivors of childhood cancer. It has been observed in survivors treated for tumors that arise in the hypothalamus and pituitary region[32] or, more commonly, after RT of the hypothalamic-pituitary unit.[33] Although GHD is quite prevalent among survivors of certain pediatric cancers, data on efficacy and safety of GH treatment in this population are limited.[34-38] Moreover, because of the small size and homogenous nature of most case series it has not been possible to determine the interaction between various patient (eg, age, sex) and treatment (eg, spinal RT) variables and how they impact on the response to GH treatment.

GH Therapy and Impact on Adult Height

To address the some of the forementioned limitations, factors that contribute to final height, and change in height standard deviation scores (SDS), height at start of GH to final height were assessed in a large and heterogeneous cohort of survivors of childhood cancer treated with GH.[39] The baseline questionnaires of all 13,539 participants in the CCSS were scanned and 684 participants were identified as having possibly received treatment with GH. Through contact with the treating endocrinologist and/or the treating institution, 361 survivors were verified as having been treated or were currently being treated with GH, while 108 had never received GH therapy. For the remaining 215 survivors (31%), GH treatment status could not be determined.[40]

From among those 361 subjects treated with GH (currently or previously), 183 had completed their growth and had a documented final height. Diagnoses included: CNS tumors (n = 90), acute leukemia (n = 64), soft tissue sarcomas (n = 23), or others (n = 6; Appendix Table A3, online only).[39] The median age at diagnosis of the primary cancer was 4.6 years and the median age at start of GH treatment was 11.3 years. Mean height SDS at start of GH therapy was −2.03 ± 0.8 and the mean final height SDS was −1.48 ± 0.10 ($P < .001$). Final height SDS was positively associated with target

height and dose of GH but negatively associated with the presence of concomitant endocrinopathies and dose of spinal RT. Change in height SDS (start of GH therapy to final height) was positively associated with male sex, younger bone age at start of GH therapy, and dose of GH; presence of concomitant endocrinopathies and dose of spinal RT were negatively associated with change in height SDS. Risk factors associated with a final height ≤ -2.0 SD included lower doses of GH and exposure to higher doses of spinal RT (Fig 6).[39]

These results confirmed the findings of smaller studies demonstrating the efficacy of GH treatment in survivors of childhood cancer.[34,35,37,41-43] Study results also concur with the findings of previous studies evaluating children with idiopathic GHD, in that the use of higher doses of GH is beneficial in maximizing final height.[44-47] The CCSS study confirmed the well documented detrimental effect of spinal RT on growth and final height.[36,41,48] Although others have suggested an augmentation in final height in childhood cancer survivors who were treated with both GH and a gonadotropin-releasing hormone agonist (GnRHa),[34,38] GnRHa therapy was not associated with an increase in height SDS in this CCSS study. This may be due to the small number of patients (14 of 183) who received GnRHa and to the fact that GnRHa therapy was not prescribed in a uniform manner.

In summary, data from this CCSS ancillary study suggest that GH therapy is associated with an increase in final height in survivors of childhood cancer. Final height is maximized when GH therapy is begun at the earliest bone age that is clinically feasible, by using conventional higher doses of GH and when possible, by minimizing the dose of spinal RT.

Risks of GH Therapy

Because GH has mitogenic and proliferating properties, there has been concern that treating cancer survivors with GH might increase their risk of either disease recurrence or the development of second neoplasms (SN).[49] A number of investigators have addressed the issue of GH replacement therapy and the risk of disease recurrence, with largely negative findings.[50-52] However, since these studies were confined, almost exclusively, to survivors of CNS tumors, there remained uncertainty about the risk of disease recurrence when GH is administered to survivors of pediatric cancers other than CNS tumors. Similarly, there is only limited information on the risk of SN in childhood cancer survivors treated with GH.[53]

In our initial study, we assessed risk of disease recurrence and development of a SN in the 361 GH-treated survivors.[40] Using a time-dependent Cox regression model, adjusting for age at diagnosis and RT and chemotherapy effects, the RR of a first recurrence was 0.83 (95% CI, 0.37 to 1.86; $P = .65$) for GH-treated survivors compared to those not treated with GH. For all diagnoses, the risk of disease recurrence was not greater for GH-treated survivors compared to survivors who were not so treated. For CNS tumor survivors as a whole, as well as for medulloblastoma survivors, the risk of disease recurrence was actually significantly reduced for cases treated with GH compared to survivors not treated with GH (Table 2).[40]

There have been 16 survivors known to be treated with GH with a diagnosed SN, 15 of which occurred after the start of GH therapy. All 15 post-GH SN were solid tumors; no secondary leukemias were found (Appendix Table A4). The results revealed that, after adjusting for age at diagnosis, sex, RT, and alkylating agent effects, the RR of a SN for GH-treated survivors compared to those not treated with GH was 3.21 (95% CI, 1.88 to 5.46; $P < .0001$; Appendix Fig A1, online only).[40] The RR of developing an SN was elevated for the entire cohort of GH treated survivors (RR, 3.21), although the overall increased risk was driven, in large part, by a small excess number of SN observed in the subgroup of acute leukemia survivors (RR, 4.98) (Table 3). The risk of death was similar between survivors who were treated with GH and those who were not.

Of concern, osteogenic sarcoma occurred in three of the 122 leukemia/lymphoma survivors treated with GH, whereas only two cases of osteogenic sarcoma were recorded in the more than 4,500 leukemia/lymphoma survivors in CCSS who did not receive GH replacement therapy. There was also marginal evidence for GH-treated survivors of CNS tumors to develop an increased number of tumors, mostly meningiomas (Table 3). However, due to the small number of events and the wide confidence intervals, we felt that the data needed to be interpreted with caution.[40]

To clarify further the association between GH therapy and the development of SN, an updated analysis was conducted of the same cohort after an additional 32 months of follow-up.[54] During the extended follow-up, five new SN developed in survivors treated with GH, for a total of 20 SN, and all were solid tumors (Appendix Table A4). Meningiomas were the most common SN (n = 9) among the GH-treated group. There were no secondary leukemias found in this updated analysis, as was the case in the previous report.[40] No new SN

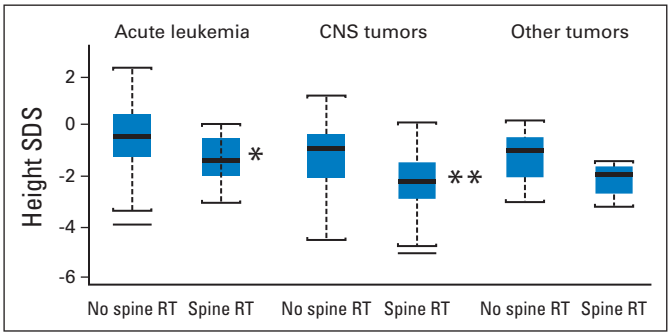

Fig 6. Final height standard deviation score (SDS) according to original diagnosis and exposure to direct spinal radiation therapy (RT). (*) $P < .05$; (**) $P < .0001$.

Table 2. Multivariate Analysis of Risk of Disease Recurrence in Patients Treated With GH by Initial Diagnosis[40]

Diagnosis	RR	95% CI	*P*
CNS tumors	0.31	0.13 to 0.77	.01
Medulloblastoma	0.13	0.02 to 0.94	.04
Astroglial	0.98	0.35 to 2.75	.96
Ependymoma	0*	0 to 13	.41
Germ cell	†		
Acute leukemia	0.85	0.12 to 6.14	.87
Rhabdomyosarcoma	0[1]	0 to 4	.31
Neuroblastoma	0[1]	0 to 35	.73

Abbreviations: GH, growth hormone; RR, relative risk.
*No recurrences occurred after GH therapy in patients in these diagnostic groups and, thus, the RR estimate is 0. The 95% CIs are calculated using the offset method in the time-dependent Cox model.
†No recurrences occurred in either the GH- or non–GH-treated groups, therefore, the RR cannot be determined.

Table 3. Multivariate Analysis of Risk of Second Neoplasm in Patients Treated With Growth Hormone by Initial Diagnosis[40]

Diagnosis	RR	95% CI	*P*
Acute leukemia	4.98	1.95 to 12.74	< .001
CNS tumors	2.34	0.96 to 5.70	.06
CNS tumors (meningiomas excluded)	1.46	0.31 to 6.79	.69
Rhabdomyosarcoma	1.82	0.41 to 8.01	.43

Abbreviation: RR, relative risk.

was reported among survivors of acute leukemia. The RR of GH-treated survivors developing an SN, as compared with non–GH-treated survivors, was 2.15 (95% CI, 1.3 to 3.5; $P < .002$; Fig 7). There was no clear association between dose and duration of GH therapy and the risk of developing a SN ($P = .1$ and $P = .8$, respectively),[54] and no difference in risk of death in GH-treated survivors compared to those not treated.

Of the SN observed among CCSS survivors treated with GH, meningiomas were the most common. Meningiomas are known to develop after RT to the head for benign and malignant conditions. For survivors of CNS tumors, meningiomas are among the most common SN observed after RT to the brain.[55-57] Since meningiomas may remain asymptomatic for prolonged periods of time, the possibility of surveillance/detection bias needs to be considered when interpreting the results.

In conclusion, data from the CCSS confirm and extend previous studies that have failed to demonstrate an increased risk of cancer recurrence in survivors of childhood cancer treated with GH.[43,45,58] While treatment with GH may increase the risk of a childhood cancer survivor developing a secondary solid tumor, the data do not support an increased risk of developing secondary leukemias.[59] Finally, the updated analysis indicated that the elevation of risk of developing a SN due to GH use appears to decrease with increasing length of follow-up, and the overall risk remains small. This risk should be weighed against the potential benefits of GH therapy in cancer survivors. These findings, however, could change over time and indicate a need for continued surveillance of childhood cancer survivors who are treated with GH.

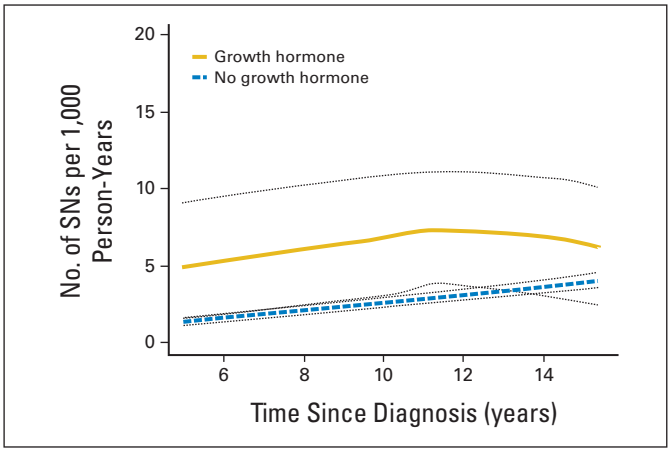

Fig 7. Comparison of the number of second neoplasm (SN) estimated per 1,000 person-years for survivors who did and did not receive treatment with growth hormone, plotted against time since diagnosis (years). (gray line) 95% CI.

DISORDERS OF BODY WEIGHT

Body mass index (BMI), a surrogate of adiposity, has been progressively increasing in the American population.[60-63] Obesity is associated with the development of endocrine, pulmonary, gastrointestinal, musculoskeletal, and cardiovascular disease.[64,65] Individuals with obesity, defined as a BMI of ≥ 30 kg/m2, have an increased risk of death due to all causes compared to individuals with a normal BMI of 20 to 25 kg/m^2.[62,64-67] Data from the CCSS were analyzed to determine the distribution of BMI in survivors of common pediatric malignancies and to identify factors associated with abnormal BMI.

BMI distribution was analyzed using self-reported heights and weights of 7,195 adult survivors who completed the CCSS baseline questionnaire (Table 4).[68] Survivors of leukemia were more likely to be obese compared to population norms (females: odds ratio [OR], 1.5; 95% CI, 1.2 to 1.8; males: OR, 1.2; 95% CI, 1.0 to 1.5). Given the significant increase in rates of obesity in the general population and the reports of increased obesity in ALL survivors and some brain tumor survivors, a surprising finding in the study was that survivors of other cancer types were more likely to be underweight, and not more likely to be obese, when compared to the general population of similar age.[68] Figure 8 depicts the sex-specific BMI distributions for underweight (≤ 18.5 kg/m^2), normal weight (range, 18.5 to 24.9 kg/m^2), overweight (range, 25 to 29.9 kg/m^2), and obese (≥ 30 kg/m^2) in CCSS survivors for each of the major childhood cancer diagnoses compared to the general population. Specifically, survivors more likely to be underweight included: female and male survivors of HD (OR, 1.7; 95% CI, 1.3 to 2.3; and OR, 3.5; 95% CI, 2.3 to 5.3); Wilms' tumor (OR, 1.8; 95% CI, 1.2 to 2.8; and OR, 5.5; 95% CI, 3.1 to 9.7); female survivors of bone cancer without amputation (OR, 1.9; 95% CI, 1.2 to 2.9); and male survivors of leukemia (OR, 2.4; 95% CI, 1.6 to 3.6), brain tumors (OR, 2.7; 95% CI, 1.6 to 4.4), non-Hodgkin's lymphoma (OR, 3.1; 95% CI, 1.9 to 5.2), neuroblastoma (OR, 4.9; 95% CI, 2.48 to 10.0), and soft tissue sarcoma (OR, 3.5; 95% CI, 2.0 to 6.0). Treatment with TBI, alkylating agents, or anthracyclines was associated with being underweight in females. In males, treatment with abdominal RT, younger age at treatment, or treatment with anthracyclines or alkylating agents was associated with being underweight. Underweight survivors were more likely to report adverse health and major medical conditions, although we could not assess whether underlying conditions were the cause or the consequence of weight status.

Female ALL survivors were more likely to be obese than male ALL survivors.[69] Significantly higher risk for obesity was found in ALL survivors who received ≥ 20 Gy of cranial RT and were younger at diagnosis: 0 to 4 years at diagnosis, females (OR, 3.8; 95% CI, 2.34 to 5.99) and males (OR, 3.19; 95% CI, 2.07 to 4.82); 5 to 9 years at

Table 4. Relative Odds of Being Underweight or Obese in Adult Survivors of Childhood Cancer Compared With Population Norms Adjusted for Age in Years[68]

	BMI					
	< 18.5			≥ 30		
Characteristic	OR	95% CI	*P*	OR	95% CI	*P*
Female						
Acute lymphoblastic leukemia	0.6	0.4 to 0.9	.006	1.5	1.2 to 1.8	.001
Other leukemia	1.2	0.6 to 2.1	.58	1.1	0.7 to 1.7	.59
Brain tumors	1.3	0.9 to 1.9	.13	1.3	1.0 to 1.6	.06
Hodgkin's disease	1.7	1.3 to 2.3	.001	0.8	0.6 to 1.0	.02
Non-Hodgkin's lymphoma	1.6	0.9 to 2.5	.09	0.5	0.3 to 0.8	.004
Wilms' tumor	1.8	1.2 to 2.8	.003	0.6	0.4 to 1.0	.04
Neuroblastoma	1.5	0.9 to 2.7	.15	0.8	0.4 to 1.3	.34
Soft tissue sarcomas	1.4	0.9 to 2.1	.09	0.7	0.5 to 1.0	.05
Bone malignancies						
No amputation	1.9	1.2 to 2.9	.008	0.5	0.3 to 0.8	.006
Male						
Acute lymphoblastic leukemia	2.4	1.6 to 3.6	.001	1.2	1.0 to 1.5	.02
Other leukemia	1.6	0.5 to 5.0	.45	0.8	0.5 to 1.3	.42
Brain tumors	2.7	1.6 to 4.4	.001	0.9	0.7 to 1.2	.50
Hodgkin's disease	3.5	2.3 to 5.3	.001	0.8	0.5 to 1.0	.06
Non-Hodgkin's lymphoma	3.1	1.9 to 5.2	.001	0.7	0.5 to 0.9	.007
Wilms' tumor	5.5	3.1 to 9.7	.001	0.6	0.3 to 1.0	.04
Neuroblastoma	4.9	2.4 to 10.0	.001	0.4	0.1 to 0.8	.01
Soft tissue sarcomas	3.5	2.0 to 6.0	.001	0.8	0.5 to 1.1	.11
Bone malignancies						
No amputation	2.1	0.9 to 5.3	.10	0.7	0.5 to 1.1	.17

Abbreviations: BMI, body mass index; OR, odds ratio.

diagnosis, females (OR, 2.3; 95% CI 1.4 to 3.5); and 10 to 14 years at diagnosis, females (OR, 2.16; 95% CI, 1.1 to 2.6). Figure 9 is a scatterplot for unadjusted BMI by age at diagnosis of ALL for females treated with ≥ 20 Gy.

Two additional analyses of ALL survivors enrolled in the CCSS include a longitudinal assessment of rate of BMI change and an etiologic study analyzing molecular variation in the leptin receptor gene in association with obesity. Garmey et al assessed the rate of BMI increase

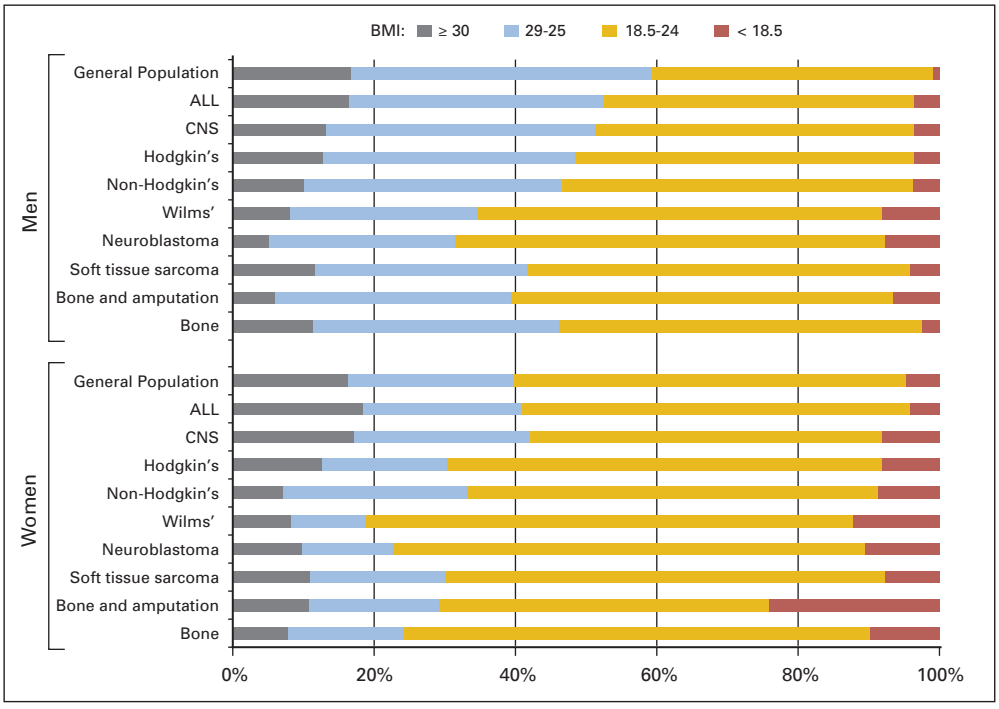

Fig 8. Percent of male and female survivors by primary diagnosis and body mass index category. ALL, acute lymphoblastic leukemia.

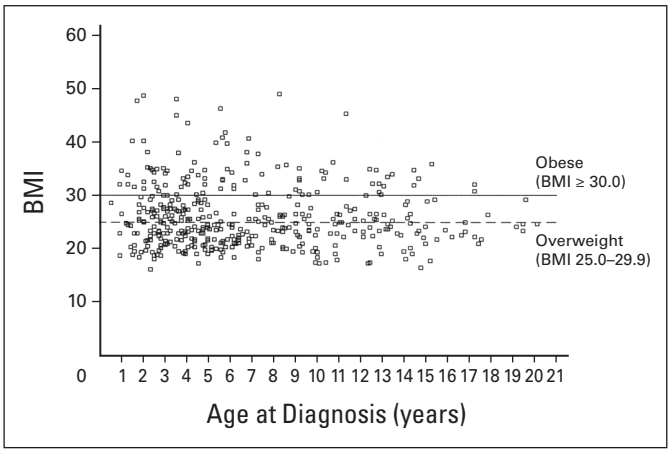

Fig 9. Scatterplot for unadjusted body mass index (BMI) by age at diagnosis of acute lymphoblastic leukemia for females treated with ≥ 20 Gy cranial radiotherapy.

in 1,451 ALL survivors compared to a sibling comparison group at baseline and at follow-up (mean interval, 7.8 years; mean age at follow-up, 32.3 years).[70] The rate of BMI increase was significantly greater in female ALL survivors treated with any cranial RT compared to the female sibling comparison group. The rate of BMI increase was statistically significantly greater in those females diagnosed with ALL at an earlier age (0 to 9 years *v* 10 to 20 years at diagnosis). A statistically significantly increased rate of change in BMI was also noted for male ALL survivors who had been treated with cranial RT in the younger age group at diagnosis compared to siblings, albeit to a lesser degree than was observed for females. There was no statistical difference in rate of BMI increase in those ALL patients not treated with cranial RT. Other studies have reported an increase in BMI from diagnosis to end of therapy in females but then a stabilization of BMI, while males demonstrate a slower but progressive increase in BMI to final height.[71-73]

In an attempt to define molecular mechanisms that may predispose a subset of ALL survivors to obesity after cranial RT, Ross et al genotyped the Leptin receptor in 600 non-Hispanic white ALL survivors enrolled in the CCSS cohort.[74] Female survivors with BMI ≥ 25 mg/kg/2 (overweight and obesity) were more likely than those with a BMI lower than 25 to have a polymorphism resulting in homozygous Arg allele at Gln223Arg—a polymorphism that has been associated with obesity in other populations.[75-77] Female survivors with Arg/Arg who were treated with ≥ 20 Gy cranial RT were six times more likely to be overweight or obese compared to those with the Gln allele. Identification of high-risk populations may allow for more focused intervention studies for primary and secondary prevention of obesity.

Female brain tumor survivors enrolled in the CCSS were also found to be at increased risk for obesity if they were younger at the time of diagnosis and had received hypothalamic RT ($P < .001$).[78] It is important to note that one group of brain tumor survivors known to be at high risk for obesity—survivors of craniopharyngioma[79-81]—were not included in the CCSS eligibility criteria, so the overall obesity outcome in brain tumor patients is likely to be underestimated in CCSS studies.

ALTERATIONS IN PUBERTAL DEVELOPMENT

Alterations in pubertal timing have been examined within CCSS. Approximately 1,000 female ALL survivors who were premenarchal at time of ALL diagnosis were compared with a similar number of female siblings with respect to self-reported age at menarche.[82] Among survivors, 4.0% reported early menarche (age < 10 years) and another 3.8% reported late menarche (age > 16 years), compared with 1.2% and 2.0% of siblings, respectively. These age cutoffs corresponded to 2.5 standard deviations from US population norms.[83]

Treatment risk factors for early menarche included any cranial RT (OR, 6.2; 95% CI, 2.1 to 18.5) or craniospinal RT (OR, 8.6; 95% CI, 1.9 to 38.6) compared with survivors treated with chemotherapy alone (Fig 10). Girls exposed to lower than 20 Gy and 20 to 30 Gy RT were equally at risk. Earlier pubertal onset may be the result of radiation-induced HPA injury. In other studies, children with non-HPA brain tumors treated with higher dose cranial RT also have an increased risk of precocious puberty.[84,85] However, with cranial doses ≥ 50 Gy, there is an increased risk of gonadotropin deficiency and pubertal delay.[86]

ALL survivors treated with craniospinal RT also were at risk for late menarche (OR, 4.8; 95% CI, 1.4 to 16.7) compared with nonirradiated ALL survivors, perhaps secondary to radiation scatter to the ovaries.[82] Abdominal RT, which is no longer part of contemporary therapy, was associated with a two-fold increased risk of late menarche, but estimates were imprecise, as fewer than 2% of patients were exposed. Abdominal RT for ALL was identified as an important risk factor for gonadal failure in an earlier study.[87] Younger age at diagnosis (< 5 years) also was associated independently with an increased risk of early menarche (OR, 4.9; 95% CI, 1.7 to 13.8) compared with older diagnosis age among ALL survivors.[82]

Nonirradiated survivors had a similar low risk of abnormal timing of menarche as siblings, even when stratified by alkylating agent exposure. However, the alkylator doses used in ALL therapy were relatively low (typically < 5 g/m^2) and the median age at ALL diagnosis was relatively young (4 years in this study). Another CCSS analysis found that exposure to specific alkylating agents and older age at exposure were independent risk factors for acute ovarian failure.[88]

A limitation of CCSS data is the lack of information on other pubertal milestones, especially those of boys, and it remains unclear

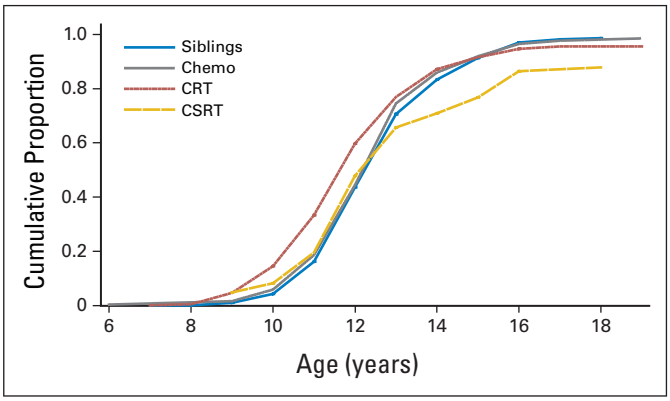

Fig 10. The proportion of women who achieve menarche over time, adjusted for ethnicity, birth year, and abdominal radiotherapy. Compared with siblings, survivors treated with chemotherapy only (chemo) did not report menarche earlier ($P = .76$), in contrast to those treated with cranial radiotherapy (CRT; $P < 0.01$). Craniospinal radiotherapy (CSRT) was associated with delayed menarche compared with siblings ($P < .01$).

whether the tempo and duration of puberty is altered in children after cranial RT. There also is evidence that girls may be more susceptible than boys to radiation-induced alterations in pubertal timing.[27]

OSTEONECROSIS

Osteonecrosis (ON), an extremely rare condition in the general population, can be a debilitating outcome of therapy in children with cancer. In this disorder, there is necrosis of one or more bone sites, usually at weigh-bearing joints, often resulting in pain and/or loss of mobility. In a 2008 CCSS report, Kadan-Lottick et al reported on the incidence of ON, as well as patient and treatment factors associated with ON.[89] Overall, there was a 20-year cumulative incidence of 0.43% and RR of 6.2 (95% CI, 2.3 to 17.2) compared to siblings, adjusted for age and sex (Fig 11). When survivors of ALL were examined separately, the 20-year cumulative incidence was 0.2% in individuals younger than 10 years at diagnosis and 2.8% in patients 16 years or older. Contrary to previous reports that described ON as an acute effect of therapy generally not reported after the first few years of exposure,[90,91] the cumulative incidence was found to increase with time for many years after treatment.

Of those CCSS cases affected, 60% had ON in more than one joint. The most common sites of ON were the hips (72%), followed by the shoulders (24%) and knees (21%). ON occurred at the RT treatment site in 44% of the cases. Thirty-three percent of survivors with ON had difficulty walking and 41% currently had pain at rest in the affected bones.

Compared with siblings, the RR was greatest among survivors of stem-cell transplantation for ALL, AML, and chronic myelogenous leukemia (RR, 26.9, 66.5, and 93.1, respectively). Nontransplant patients with ALL (RR, 6.5; 95%, 2.2 to 19.4), AML (RR, 11.2; 95% CI, 2.1 to 61.2), and bone sarcoma (RR, 7.3; 95% CI, 2.0 to 26.2) were also at higher risk.

Older age at diagnosis, shorter elapsed time, exposure to dexamethasone (with or without prednisone), and gonadal and nongonadal RT were independently associated with ON. Cases who were ≥ 16 years at diagnosis were 6 times more likely than those 0 to 4 years at diagnosis to develop ON ($P < .001$). Figure 12 displays the increasing cumulative incidence with older age at diagnosis. Dexamethasone with or without prednisone appeared to confer a higher RR of ON than prednisone alone (2.7, 95% CI, 1.2 to 6.4 *v* 1.5, 95% CI, 0.5 to 4.3).

Estimates of ON from the CCSS study fall in the low end of reported incidence rates. Overall estimates for the incidence of ON have ranged from approximately 1% to 9%,[90,92,93] when based on clinical presentation, to approximately 15% based on magnetic resonance imaging screening.[94] Because the CCSS study relied on self-report, as opposed to the medical record or magnetic resonance screening, there may have been an underestimation of the incidence of ON. However, the rate reported from the CCSS cohort may be a reasonable reflection of the true burden of disease, rather than acute toxicity, because the major morbidities resulting from ON are unrelieved discomfort and decreased ambulatory mobility. These are symptoms that are amenable to self-report.[95,96] Reported rates in the CCSS may also have been lower because of differences in therapy in the treatment era of the cohort (1970 to 1986).

Most of the findings of risk factors for ON among CCSS cases were confirmatory of prior studies. Previous investigators identified an increased incidence of ON in childhood cancer survivors with a history of stem-cell transplantation,[97-99] radiation exposure,[100] glucocorticoid therapy,[93] and adolescent age at diagnosis.[93,94,98,101] The markedly elevated relative risk of ON among recipients of allogeneic stem-cell transplantation has been ascribed to long-term glucocorticoid therapy, which is used to treat chronic graft-versus-host disease, rather than exposure to radiation.[98,99] From the available reviewed literature, hypogonadism has not been previously reported as a risk factor for ON. Our observation that RT to the gonads was an independent risk factor for ON will need to be verified in future studies in which gonadal function is directly assessed.

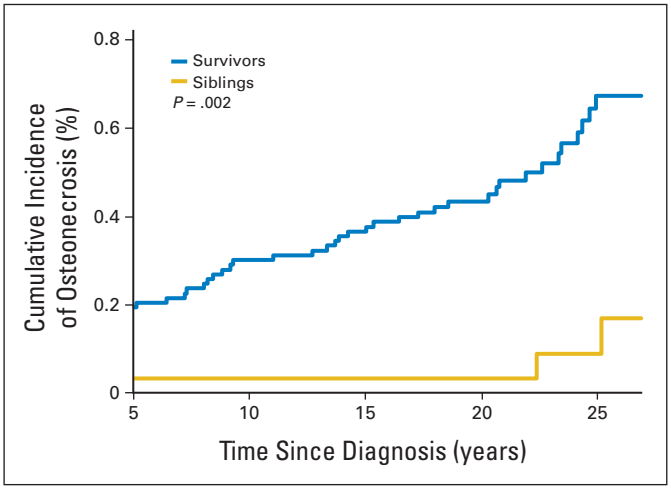

Fig 11. Cumulative incidents of osteonecrosis among survivors and a sibling comparison group starting 5 years after diagnosis.

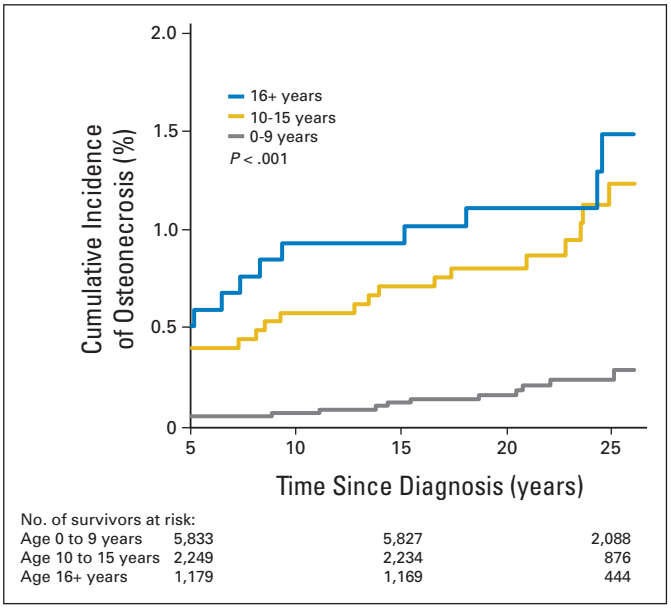

Fig 12. Cumulative incidence of osteonecrosis among all survivors stratified by age at diagnosis.

CARDIOPULMONARY DISEASE

Cardiovascular Disease

Cardiovascular disease can be a serious complication after cancer therapy. Cardiac mortality in the CCSS has been reported to be seven-fold higher (standardized mortality ratio [SMR], 7.0; 95% CI, 5.9 to 8.2) than expected from an age-matched general population.[102] A variety of cardiovascular complications have become apparent among cancer survivors including dilated cardiomyopathy, myocardial infarction, valvular abnormalities, and pericarditis.

To date, reports from the CCSS have identified survivors of brain tumors, leukemia, rhabdomyosarcoma, and lymphoma to be at particularly high risk for adverse cardiovascular outcomes. Gurney et al[24] identified that 18% of childhood brain tumor survivors reported a heart or circulatory late effect. Risk was highest among those treated with surgery, RT, and chemotherapy compared to surgery and RT alone, suggesting a potential additive vascular injury from chemotherapy.[24] Among ALL survivors in the CCSS cohort reporting a chronic medical condition, the risk of reporting a cardiac condition was nearly seven-fold higher compared to the siblings (OR, 6.9; 95% CI, 4.2 to 12.9) and highest among those treated for relapsed disease compared to nonrelapsed ALL survivors (OR, 2.8; 95% CI, 1.5 to 4.9). No significant association was identified based on radiation exposure.[3] A similar analysis among AML survivors in the cohort found the 20-year cumulative incidence of cardiac disease to be 4.7% (95% CI, 2.1 to 7.3) with an SMR of 9.1 (95% CI, 1.0 to 32.7). This particular analysis excluded survivors treated with stem-cell transplantation.[4]

Twenty-one percent of rhabdomyosarcoma survivors reported one or more cardiac sequelae; the majority occurred long after treatment and were distributed among the various primary tumor sites. Compared to siblings, the risk was elevated more than 5 years after diagnosis for congestive heart failure (RR, 43.0; 95% CI, 12.7 to 145.5) and angina-like symptoms (RR, 2.0; 95% CI, 1.3 to 2.9).[5] Among survivors of non-Hodgkin's lymphoma the SMR for cardiac disease was 6.9 (95% CI, 3.1 to 13.0).[103] Cardiovascular disease in survivors may also be associated with other late sequelae. Of twenty-four HD survivors who reported a stroke, one half also reported a cardiac event (arrhythmia, valvular disease, or congestive heart failure). The authors conclude that carotid vascular injury or cardiac valvular disease may contribute to the risk of stroke among these survivors.[2,104]

Improvements in molecular biology have increased the ability to potentially identify genetic factors that may increase the risk for late adverse sequelae. Polymorphisms of the carbonyl reductase 3 (*CBR3*) and nicotinamide adenine dinucleotide phosphate: guinone oxidoreductase 1 (*NQO1*) genes are hypothesized to increase cardiotoxicity by altering anthracycline pharmacodynamics. In a nested case-control study among survivors exposed to anthracyclines, CCSS investigators analyzed DNA from 30 survivors with congestive heart failure and 115 matched controls. After adjusting for sex and primary disease, no association with *NQO1* was identified but a trend was suggested between congestive heart failure and the *CBR3* genotype (OR, 8.2, $P = .056$ for G/G *v* A/A, OR, 5.4, $P = .092$ for G/A *v* A/A).[105] As one of the first studies to investigate potential genetic predispositions to anthracycline-induced cardiotoxicity, this study emphasizes the need for ongoing basic and clinical research to elucidate the pathophysiology of late cardiovascular outcomes. Improved understanding of the biology of cancer late effects will create opportunities to develop therapeutic interventions designed to ameliorate or prevent these adverse outcomes.

Pulmonary Disease

Pulmonary function has been shown to be compromised by anticancer therapy. The lung is one of the most radiation-sensitive structures in the body, and the late phase of radiation injury is characterized by pulmonary fibrosis, which is usually asymptomatic; however, when symptomatic, it presents with dyspnea and a nonproductive cough. Recent studies have also suggested that RT to the lung increases the subsequent risk of lung cancer, with the risk continuing to increase with time after exposure.[106] Pulmonary toxicity due to chemotherapy, like that associated with RT, presents with late-onset pulmonary fibrosis. Chemotherapy-induced lung fibrosis in childhood may remain asymptomatic for many years but become symptomatic at any time.[107]

Based on subject self-report, the CCSS identified a high incidence of significant pulmonary pathology including chronic cough and shortness of breath, recurrent pneumonia, pleurisy, lung fibrosis, and use of supplemental oxygen among childhood cancer survivors.[108] These adverse pulmonary outcomes were significantly associated with treatment-related factors. In the time period of 5 or more years after diagnosis, emphasizing the first occurrence of a late phase pulmonary toxicity, statistically significant associations were present for: lung fibrosis and chest RT (RR, 4.3; $P < .001$); supplemental oxygen use and chest RT (RR, 1.8; $P < .001$); supplemental oxygen use and specific chemotherapy agents—carmustine (RR, 1.4; $P = .05$), bleomycin (RR, 1.7; $P = .001$), busulfan (RR, 3.2; $P = .002$), lomustine (RR, 2.1; $P < .001$), cyclophosphamide (RR, 1.5; $P = .05$); recurrent pneumonia and chest RT (RR, 2.2; $P = .001$); recurrent pneumonia and cyclophosphamide (RR, 1.6; $P = .04$); chronic cough and chest RT (RR, 2.0; $P < .001$); chronic cough and specific chemotherapy agents—bleomycin (RR, 1.9; $P < .001$) and cyclophosphamide (RR, 1.3; $P = .004$); pleurisy and chest RT (RR, 1.4; $P = .02$); pleurisy and busulfan (RR, 5.1; $P = .02$). As suggested in the literature, self-reported pulmonary conditions continue to manifest more than 5 years after diagnosis; specifically, the cumulative incidence continues to increase for lung fibrosis up to 15 to 25 years after diagnosis for those who received chest RT both with and without pulmonary-toxic chemotherapy (Fig 13). Chest RT only was associated with a 5.3% cumulative incidence of lung fibrosis at 20 years after diagnosis.

Cause-specific mortality due to pulmonary toxicities has also been documented in this cohort.[1] Where the cause of death was known, 2.6% were due to respiratory complications, which yielded an eight-fold increased risk (SMR, 8.8; 95% CI, 6.8 to 11.2) when compared to age-and sex-matched population norms. In addition, there were 19 deaths reported due to lung cancer.

NEUROLOGIC AND NEUROSENSORY DISORDERS

Long-term neurologic sequelae in childhood cancer survivors have varied manifestations and can occur in survivors of many different types of cancer. Survivors of childhood brain tumors are at highest risk of neurological compromise and have been the most extensively studied.

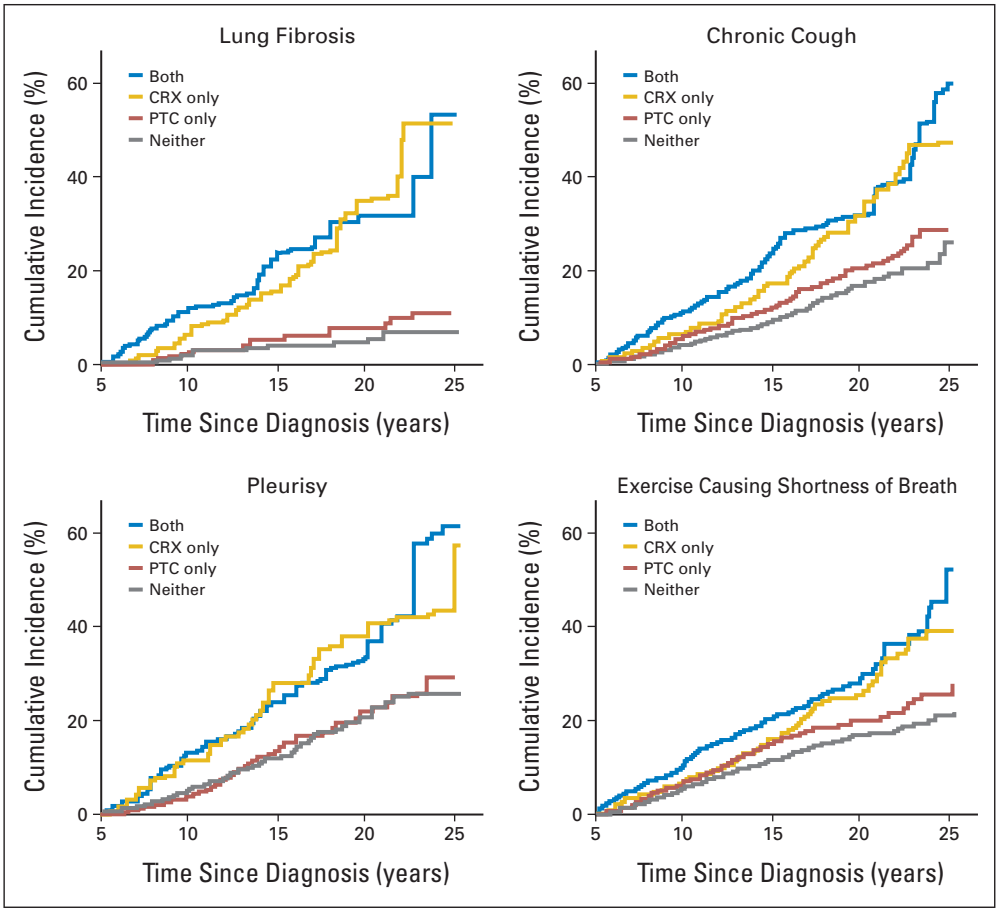

Fig 13. Cumulative incidence of medical conditions reported ≥ 5 years after diagnosis. CRX only, chest radiation therapy only; PTC only, pulmonary toxic chemotherapy only; Both, CRX and PTC; Neither, neither CRX nor PTC.

Neurologic Outcomes in Brain Tumor Survivors

Late-onset neurologic sequelae in brain tumor survivors often occur in the setting of residual effects of earlier damage from the primary tumor itself, its surgical removal, or from the associated RT or chemotherapy treatment. This can make understanding the timing of onset of neurologic compromise difficult. Causation may be difficult to ascertain due to the relatively high incidence of recurrence and second malignancies encountered in this patient population.

Long-term neurologic deficits in childhood brain tumor survivors include: neurosensory impairments, such as hearing loss, tinnitus, cataracts and other vision problems; seizures or convulsions; and relatively poorly-defined coordination or motor control difficulties.[109] The CCSS study has confirmed that these types of complications are quite frequent relative to a sibling comparison group (Table 5), and that neurologic complications are as likely to occur in children with astroglial tumors as in those surviving medulloblastomas. For example, seizure disorders were reported in 25% of brain tumor survivors in the CCSS, including 6.5% who had a first reported occurrence of seizures 5 or more years after diagnosis. The likelihood of a seizure was associated with a radiation dose of at least 30 Gy to any cortical segment of brain, but not to a specific histological subtype of tumor.[109] Similarly, the likelihood of hearing loss, which occurred in 12% of CCSS brain cancer participants overall and as a late occurring adverse effect in 3% to 4% of these survivors, was associated with radiation exposure of 50 Gy or more that included the posterior fossa, (an area that includes the hearing apparatus). However, the likelihood of hearing loss was not affected by initial tumor type.[109]

Stroke is a potentially devastating but relatively uncommon neurologic complication in children with brain tumors, occurring at an incidence of 267 cases per 100,000 person-years in the CCSS cohort. Overall, 63 (3.4%) of 1,871 brain tumor survivors reported a late-occurring stroke.[2] Children surviving brain tumors for 5 years or longer in CCSS were 29 times more likely than the sibling comparison group to report a stroke occurrence, and cranial RT in doses of ≥ 30 Gy was associated with increased risk of stroke in a dose-dependent fashion. Among brain tumor survivors receiving RT , alkylating agents appeared to enhance the risk of stroke, while other chemotherapeutic agents did not. The impact of stroke on overall health and quality of life in the survivor population has not been well characterized. However, a recent unpublished analysis of brain tumor patients in the CCSS revealed that patients who had a history of stroke, as well as those with paralysis and hearing deficits, were more likely to have neurocognitive difficulties (L. Ellenberg, personal communication, August 2008).

Risk analysis of chronic neurologic sequelae in brain tumor survivors in the CCSS cohort is limited to patients diagnosed between 1970 and 1986. It is not clear that the more recently treated brain tumor patients will have similar long-term chronic neurologic conditions. For some types of brain tumors, therapy has dramatically changed over the past two decades, with less RT being used for infants and young children with low-grade gliomas, and reduced doses of craniospinal RT employed for some subsets of children with medulloblastoma. It is unclear how modern treatment modifications will differentially impact on the type and frequency of neurologic sequelae

Table 5. Incidence Rates and Relative Risks by Time Period of Onset of Adverse Neurologic Outcomes[109]

Parameter	Neurosensory Deficits						Focal Neurologic Dysfunction		
	Any Hearing Impairment	Tinnitus	Persistent Dizziness	Legal Blindness in One or Both Eyes	Cataracts	Problems With Double Vision	Any Coordination Problem	Any Motor Problem	Any Seizure Disorder
Reported outcome									
Yes*									
No.	192	171	155	211	48	278	784	425	401
%	12	11	10	13	3	17	49	26	25
No†									
No.	1,402	1,422	1,439	1,384	1,557	1,315	757	1,159	1,114
%	87	88	90	86	97	82	47	72	69
Diagnosis to end of treatment, yes									
No. of patients	46	45	76	92	6	130	408	196	141
Rate‡	16.6	15.9	25.5	32.8	2.0	43.7	189.4	79.7	54.4
95% CI	12.4 to 22.1	11.8 to 21.4	20.2 to 32.2	26.5 to 40.5	0.9 to 4.5	36.4 to 52.5	170.7 to 210.2	69.3 to 91.6	45.9 to 64.5
RR§‖	42.8	17.2	44.9	93.2	9.8	123.5	158.8	121.4	55.3
95% CI	27.1 to 67.5	11.8 to 25.0	32.1 to 62.9	59.8 to 145.4	3.9 to 24.6	83.6 to 182.3	127.2 to 198.4	92.7 to 159.0	41.5 to 73.6
End of treatment to 5 years after diagnosis, yes									
No. of patients	58	33	26	77	11	73	189	94	101
Rate‡	9.4	7.2	6.2	14.8	2.2	17.1	67.0	21.6	23.1
95% CI	7.3 to 12.1	5.2 to 9.8	4.6 to 8.5	12.0 to 18.3	1.2 to 3.8	13.9 to 20.9	59.4 to 75.6	18.1 to 25.9	19.3 to 27.6
RR§‖	26.7	7.0	9.6	55.1	11.2	43.5	60.2	35.8	24.7
95% CI	17.4 to 40.9	4.8 to 10.2	6.4 to 14.3	34.6 to 87.8	5.4 to 23.4	29.2 to 64.9	47.8 to 75.9	26.6 to 48.3	18.5 to 33.1
5 years after diagnosis to end of follow-up, yes									
No. of patients	76	59	35	19	22	41	74	85	105
Rate‡	5.9	5.4	2.9	1.9	1.7	3.9	11.8	7.6	10.3
95% CI	4.8 to 7.4	4.3 to 6.9	2.1 to 4.0	1.3 to 2.8	1.1 to 2.5	3.0 to 5.3	9.5 to 14.7	6.1 to 9.3	8.5 to 12.4
RR§‖	17.3	3.7	3.2	14.8	11.9	8.8	12.6	12.4	12.6
95% CI	11.6 to 25.8	2.7 to 5.1	2.2 to 4.8	7.5 to 29.2	5.7 to 24.8	5.6 to 13.8	9.1 to 17.5	8.7 to 17.5	9.2 to 17.1

Abbreviation: RR, relative risk.
*Excludes conditions prior to diagnosis.
†Includes "not sure" and missing responses.
‡Rate per 1,000 person-years.
§Adjusted for sex; relative to siblings.
‖$P < .0001$.

from brain cancer. Furthermore, the use of new targeted RT delivery techniques may impact the late recurrence risk and type of late sequelae in brain tumor survivors. Chemotherapy, which was not routinely used for children with brain tumors between 1970 and 1986, is now an accepted component of treatment for most children with medulloblastoma and other primitive neuroectodermal tumors, and in young infants with either nonmalignant or malignant tumors. Cisplatinum, an agent that can cause significant ototoxicity, especially when coupled with RT, was not used widely until the early 1990s for brain cancer, and the addition of this drug in modern therapy will likely result in increased sequelae, specifically sensorineural hearing loss. The wider use of high-dose alkylator therapy and anthracyclines may also result in a greater incidence of late onset organ damage.

Neurologic Outcomes in Survivors of Hematologic Malignancies

Survivors of childhood brain tumors are not the only population at risk for late neurologic sequelae. In particular, survivors of HD and leukemia are at increased risk of late-occurring stroke (> 5 years after diagnosis) and its resultant neurological damage. In the CCSS cohort, the rate of late-occurring stroke was reported at 83.6 per 100,000 person-years in HD survivors, and 58 per 100,000 person-years in leukemia survivors.[2,104] Among leukemia survivors, RRs compared to the sibling group were elevated both for those who received (RR, 5.9; $P < .001$) and did not receive cranial RT (RR, 4.0; $P = .01$), and the RR for stroke was highest for those who had had relapsed leukemia (RR, 21; $P < .001$).[2]

The relative risk of stroke among HD survivors was 4.3 compared with siblings, and was highly associated with exposure to RT to the chest and neck (Appendix Table A5, online only). The median interval from HD diagnosis to stroke occurrence was 17.5 years. Neither chemotherapy nor splenectomy appeared to be associated with stroke risk. The incidence rate for late stroke among those treated with mantle RT was 109.8 per 100,000 person years, and the cumulative incidence continued to increase substantially even 25 years after diagnosis, where it reached nearly 6%,[104] demonstrating the continued need for surveillance long after treatment in completed, perhaps throughout the survivor's entire life.

Children with a history of leukemia are also at increased risk for neurosensory deficits, focal neurologic deficits, late onset seizures, and

headaches. Mody et al reported that 2.4% of survivors of ALL had an adverse neurologic outcome (RR, 5.3; $P < .001$) when compared with the sibling group.[3] The elevated risk for neurologic outcome is much higher for leukemia survivors after relapse, when compared to those who had no history of relapse (RR, 3.2; $P < .001$).

The incidence of late-occurring neurologic compromise has not been thoroughly studied in most other survivor populations. The frequency of other types of neurologic compromise, such as peripheral neuropathy, headaches, or dizziness, have not been fully elucidated, and their impact, occurring in an isolated fashion or in addition to other sequelae, may significantly affect the quality of life of survivors and resultant psychosocial outcomes. Another factor which will need to be taken into account as survivors who had received RT age into and throughout adulthood, is the increased relative likelihood of developing treatment-related meningiomas, resulting in further morbidity, including late neurologic sequelae.[110]

CONCLUSION

Observations by the Childhood Cancer Survivor Study provide a unique profile of the health of survivors of childhood cancer and of the chronic diseases they face. CCSS cohort analyses benefit from large sample size, geographic diversity, long length of follow-up, and near-complete information on primary cancer treatment delivered at multiple institutions. Use of a sibling comparison group has allowed investigators to estimate the magnitude of the burden of health problems in the cohort. Nonetheless, CCSS's characterization of chronic disease in childhood cancer survivors has several limitations. Self-reported outcomes are subject to both under-reporting and over-reporting; validation of self-report with medical record documentation is difficult and due to our restricted resources not feasible for the majority of outcomes. CCSS investigators do not have access to survivors' current medical records, resulting in possible misattribution of risk. For example, women who have had breast cancer after treatment for childhood HD may go on to develop endocrine or cardiac disease associated with their breast cancer treatment, which might in turn be attributed to their HD therapy. The possibility of surveillance bias must be considered. Conditions such as hypertension, osteopenia, and colonic polyps, for example, may appear to be more frequent in the survivor group than the comparison group as a result of more screening occurring in survivors. The cohort may not be proportionately representative of childhood cancer survivors overall. Members of minority groups are under-represented, and the cohort members, as volunteer participants, may not accurately represent the chronic disease burden of the population of survivors overall. Finally, the CCSS has focused its work thus far on patients treated between 1970 and 1986, and therefore has limited information regarding health outcomes of more modern therapies. Despite these limitations, the findings in this cohort are remarkably consistent with chronic disease reported in other survivor cohorts with much smaller sample sizes.[8,10]

The CCSS has planned several important initiatives that will expand our understanding of chronic illness in the cohort. A large collection of DNA specimens from members of the cohort has been banked, and additional specimens will be collected. This resource will allow us to collaborate with laboratory investigators to analyze genetic characteristics associated with risk for treatment-related outcomes. Not only will the identification of survivor groups at higher biologic risk for a particular outcome allow for differential screening and prevention, but it is likely to inform the design of future therapies which can be theoretically personalized based on risks. This avenue of inquiry may also result in understanding of the pathogenesis of chronic illness in the general (nonsurvivor) population; by studying survivors with rare outcomes, the genetics of common chronic illnesses, such as cardiomyopathy or stroke, may be better characterized.

Future analyses of the cohort will benefit from addition of both new cohort members and of follow-up data. The chronic conditions observed in the cohort thus far are representative of outcomes after exposure to therapies delivered between 1970 and 1986. The recent expansion of the cohort to include 5-year survivors of cancer diagnosed between 1987 and 1999 will further our understanding of the impact of more modern therapies on the development of chronic illness. These more modern therapies will include a larger group of survivors who were exposed to stem-cell transplantation and to newer agents for which there are little or no long-term follow-up data, including newer alkylators, topoisomerase inhibitors, cardioprotectants, and growth factors. In addition, as the current cohort ages, longitudinal follow-up will be critical to understanding the impact of childhood cancer treatment on the incidence and severity of adult- and geriatric-onset diseases. The analyses completed thus far are largely reports of baseline data, but risk factors for later development of specific chronic illnesses will soon be available. Other future work will include ancillary studies that validate self-reported conditions and directly measure outcomes, particularly those not amenable to self-report. Current efforts are focused on development of studies that include survivor physical examinations, and blood or other specimen procurement. Finally, analyses of chronic illness in childhood cancer survivors have been enhanced by the experts in a variety of subspecialties outside of oncology, such as endocrinology and neurology. To understand the risks for adult-onset illnesses in survivors, academic clinicians and clinical researchers in fields such as gastroenterology, nephrology, and cardiology will be particularly important collaborators.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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