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Pediatric Hodgkin Lymphoma Survivors at Negligible Risk for Significant Bone Mineral Density Deficits

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Abstract

Background: We hypothesized that pediatric Hodgkin lymphoma (HL) survivors would have bone mineral density (BMD) deficits compared to their peers because of osteotoxic chemotherapy during the time of greatest BMD accretion.

Methods: We retrospectively reviewed records of HL survivors returning for follow-up between 1990 and 2002. Of the 133 eligible survivors, 109 who underwent quantitative computed tomography (QCT) comprised the study group. QCT-determined BMD Z-scores were correlated with patient characteristics and therapeutic exposures by Wilcoxon rank sum or Chi-square tests. Logistic regression models were used to explore risk factors for diminished BMD.

Results: The study cohort was half male (50.5 %) and 85.3 % reported their race as white. Participants were representative of all survivors potentially eligible for study, except that more study participants were female, had hypothyroidism, and had received cyclophosphamide. Median age at diagnosis was 15.1 years (range, 3.1 to 20.7 years); median time between diagnosis and QCT was 7.5 years (range, 5.0 to 12.4 years). The proportion of HL survivors with BMD below the mean did not significantly differ from the general population ($P = 0.503$). However, those with BMD -1.5 SD and BMD -2.0 SD or lower (14.7% and 7.3%, respectively) exceeded that in the general population (6.7% and 2.3%, respectively; $P < 0.001$ for both degrees of severity). Males, diagnosed at 14 years or older, were at 6.5 times higher risk than females (OR 95% CI: 1.24 – 34.14; $P = 0.027$) for BMD deficits.

Conclusions: Overall, pediatric HL survivors had negligible BMD deficits. Male gender was associated with an increased risk of developing BMD deficits.

Keywords

pediatrics; Hodgkin lymphoma; bone mineral density; quantitative computed tomography

INTRODUCTION

Survivors of childhood cancer may experience long-term adverse effects related to treatment for their malignancy. One of these toxicities, low bone mineral density (BMD), increases the risk for osteoporosis, and may predispose these survivors to fractures. Deficits in BMD are well-documented among childhood acute lymphoblastic leukemia (ALL) survivors and arise from the interaction of multiple factors which include genetic predisposition [1-3], cranial irradiation [4-12], chemotherapy exposure [9,13-15,15-18], nutritional status [19-23], physical activity levels [15,20,21,23,24], and age at the onset of puberty [25-27]. Similarly, BMD deficits have been identified in children who have undergone bone marrow transplantation[14], and those treated for brain tumors[10,28] or sarcomas during childhood[16]. Although some studies have assessed BMD in adult males following treatment for Hodgkin lymphoma (HL)[29], few studies have evaluated the effects of treatment for HL on BMD in children[11,30]. In this population, multiple factors such as age at diagnosis, gender[9,31-34], lifestyle factors (e.g., smoking, physical activity, diet)[35], genetic predisposition, endocrine function[36], amount and location of radiotherapy[4], and treatment protocol may influence BMD accretion[9].

We hypothesized that, survivors of pediatric HL, like survivors of other pediatric malignancies [9,16,37], would have BMD deficits when compared to their peers, particularly because these patients are treated with osteotoxic chemotherapy during the time of greatest BMD accretion. The aims of our analysis were to assess the skeletal health of children after treatment for HL and to determine factors predictive of risk for BMD deficits. The results of this study should direct appropriate health screening for survivors of childhood HL.

METHODS

Participants

This study was approved by the Institutional Office of Human Subjects Protection and adhered to the Health Information Portability and Accountability Act of 1996. We retrospectively reviewed the records of HL survivors diagnosed between 1990 and 2002 and treated with risk-adapted combined-modality therapy, including combination chemotherapy and response-based, low-dose, involved-field radiation therapy[38-40]. BMD was assessed by quantitative computed tomography (QCT) as part of the patient's visit to St. Jude Children's Research Hospital (SJCRH) After Completion of Therapy (ACT) Clinic. The ACT Clinic provides long-term follow-up care for survivors who are 5 years from diagnosis and who maintain at least 2 years of remission following completion of therapy.

Measures

QCT—Our primary outcome of interest for these analyses was BMD QCT Z-score of the L1-L2-vertebral bodies. Participants were scanned while lying on a padded cushion that contains solid phantoms of K_2HPO_4 mineral equivalents. Mineral content was determined with direct axial images of the mid bodies of L₁ and L₂ as determined from a sagittal scout image of the upper abdomen[41,42]. BMD was determined from the average of the two vertebral bodies. Vertebral body mineral density was determined using an off-line personal computer (PC) equipped with Mindways QCT Pro software, which allows 3-dimensional

rotation of the spine for optimal examination of the regions of interest (ROIs)[42]. The ROIs were placed to include approximately one-third of the central trabecular core of bone of each vertebra. BMD results included age and sex specific manufacturer-obtained reference data, from which a patientspecific Z-score was generated[42]. We chose a Z-score of -1.5 for the risk analyses to reflect our clinical practice patterns pertaining to patient referral for interventions to improve BMD subsets. If a patient underwent multiple studies, the latest examination was chosen for analysis.

Demographic and clinical characteristics—Demographic and clinical characteristics were abstracted from medical records, both to describe the cohort and to test for their influence on the BMD outcome. Age, gender, race, time since diagnosis, height, weight, the presence or absence of hypothyroidism, the presence or absence of hypogonadism, and incident second malignancies were recorded for each participant.

Height and weight were used to calculate body mass index (BMI). We grouped the study cohort as normal, overweight, or obese, using the BMI percentiles or scores delineated in the age- and sex-specific growth charts provided by the Centers for Disease Control [<http://www.cdc.gov/nccdphp/dnpa/growthcharts/sas.htm>]. BMI thresholds for participants younger than 18 years were classified as: normal – 5th to 85th percentile, underweight – less than 5th percentile, overweight –between the 85th and 95th percentile, obese – more than the 95th percentile. BMI thresholds for participants 18 years or older were classified as: underweight – below 18.5, normal – 18.5 to 24.9, overweight – between 25 and 30, obese – over 30. For statistical analysis we grouped underweight and normal into a single category and overweight and obese into a single category for the two age categories.

Hypothyroidism was defined as levels of the thyroid stimulating hormone (TSH) above the upper limit of normal given by the evaluating laboratory, subnormal levels of free thyroxine, or the need for thyroid hormone replacement therapy. Over treatment was characterized by subnormal TSH levels (below $0.4 \mu\text{Int units/mL}$).

Hypogonadism was defined as subnormal levels of gonadal hormones (testosterone or estradiol) or levels of the luteinizing hormone (LH) above the upper limit of normal for age based on the ranges of the evaluating laboratory, both, or the need for hormonal replacement therapy. Only patients at risk for gonadal dysfunction based on treatment including alkylating agent chemotherapy or radiation to fields potentially impacting the gonads and those clinically suspected of gonadal dysfunction underwent laboratory evaluation for the same.

Treatment exposures—Total doses of chemotherapeutic agents were also abstracted from medical records. Both cyclophosphamide and procarbazine total doses had an approximately binomial distribution, with patients receiving either no cyclophosphamide or procarbazine (36.1% and 38.3% of patients, respectively) or approximately equal doses of the agents (cyclophosphamide median 3600 mg/m^2 and range, 1500 to 7335 mg/m^2 ; procarbazine median 4200 mg/m^2 and range, 2254 to 4200 mg/m^2), so exposure to these agents was categorized as yes or no. Methotrexate and prednisone exposures were also divided into two classes with methotrexate doses greater than 120 mg/m^2 (median 120 mg/m^2 and range, 0 to 24304 mg/m^2) classified into one category and doses less than or equal to 120 mg/m^2 into the other category. Prednisone doses were classified as greater than 1680 mg/m^2 and less than or equal to 1680 mg/m^2 (median 1680 mg/m^2 and range, 0 to 3360 mg/m^2).

Whether or not a participant received radiation that included the lumbar spine was also recorded and tested in the statistical models because of its potential to directly alter measured BMD.

Statistical Analysis

Demographic and clinical characteristics were summarized with descriptive statistics and compared between eligible patients who did and did not undergo QCT with Wilcoxon Rank-sum or Chi-squared tests [43]. Exact tests were used if the expected sample size was less than 5. Kruskal-Wallis test was used to compare age at diagnosis of males compared to females. Assuming QCT Z-scores to be normally distributed, we estimated the expected proportion within different percentiles (e.g. within $-1SD$ to $-2SD$) and compared these proportions with observed proportions using one sample binomial test. Univariable (simple) and multivariable (multiple) logistic regression models were used to evaluate the associations between demographic clinical and treatment parameters and a BMD QCT lumbar Z-score below -1.5 . Only factors with $P < 0.10$ in univariable models were included in the multivariable models. Statistical significance was set at $P \leq 0.05$. We did not adjust significance levels for number of comparisons because of the exploratory nature of this study. Analyses were performed using SAS, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Characteristics

There were 133 survivors of HL potentially eligible for this study. Among these potential eligible survivors, 109 had a QCT to evaluate BMD as part of a follow-up visit between July 1, 1997, and July 1, 2007. Compared to those who did not undergo QCT, study participants included a greater proportion of females (49.5% vs. 16.7%; $P = 0.003$), survivors with hypothyroidism (59.6% vs. 37.5%; $P = 0.048$), and survivors who had received cyclophosphamide (67.9% vs. 45.8%, $P = 0.042$) (Table I). Of the 109 survivors who underwent QCT measurements of BMD, 55 (50.5%) were male and 93 (85.3%) were white. The median age at diagnosis was 15.1 years (range, 3.1–20.7 years); median age at diagnosis was 14.1 years (range, 3.1–19.7 years) and 16.2 years (range, 5.8–20.7 years) for males and females, respectively ($p = 0.0011$). The median time between diagnosis and QCT was 7.5 years (range, 5.0 to 12.4 years) and the median number of years from diagnosis to last follow-up was 9.5 years (range, 5.1–13.0 years). Among the participating survivors, 65 (59.6%) had been diagnosed with hypothyroidism.

Nineteen (17.4%) patients (three females and 16 males) had clinical and/or laboratory evidence of hypogonadism. Of these patients, 3 males received pelvic/inguinal radiation therapy that could have impacted gonadal function. One female received abdominal-pelvic radiation that could potentially have affected ovarian function. Of the 19 patients, three females and two males were receiving hormone replacement therapy.

Thirty-one (28.4%) patients had received radiation fields that could potentially impact lumbar spine BMD measurement.

Distribution of Z-Scores for BMD

The proportion of HL survivors with BMD below the expected mean did not significantly differ from the general population ($P = 0.503$). However, the proportion of survivors with BMD $-1.5 SD$ or $-2.0 SD$ or lower (14.7% and 7.3%, respectively) was higher than reported in the general population matched for age and gender (6.7% and 2.3%, respectively; $P < 0.001$ for both degrees of severity). Compared to the reference population, the patient cohort had fewer than expected cases falling in the 0 to $+1 SD$ and more than

expected in the +1 to +2 SD category, but this difference was not statistically significant. In fact, the distribution of BMD Z-scores greater than +1SD in the reported population was not statistically significantly different than that expected ($p=0.135$) in age and sex-matched controls. Figure 1 shows BMD Z-score distributions for both the study population and the age-matched reference population.

An initial examination of BMD Z-scores by demographic characteristics revealed that all those with Z-scores below -1.5 were white. Further evaluation of the BMD Z-score distribution, limited to participants who reported their race as white, demonstrated estimated percentages of BMD Z-scores -1.5 SD or lower of 12.0% (95% CI: 6.5%–17.6%) and -2.0 SD or lower of 6.0% (95% CI: 2.0%–10.1%).

The results of the univariable and multivariable logistic regression models evaluating the association between demographic, clinical and treatment characteristics and a BMD Z-score less than -1.5 are shown in Table II. Male survivors were more likely than female survivors to have BMD Z-scores less than -1.5 in both univariable and multivariable ($p < 0.04$) models, when adjusted for BMI. Further, males diagnosed with HL at age 14 years or greater had a 6.5-fold (OR 95% CI: 1.24 – 34.14; $P = 0.027$) increased risk of BMD deficits falling below $Z = -1.5$. None of the other demographic, clinical or treatment characteristics were associated with BMD Z-scores below -1.5 .

DISCUSSION

In this exploratory study examining the prevalence and distribution of BMD deficits among HL survivors, we did not observe an excess of BMD deficits. This is in contrast to other studies that have shown BMD deficits in survivors of childhood cancer[4,9,11,14,16,16,30,31,34,37]. We did find that the proportion of survivors in our study with BMD -1.5 SD or -2.0 SD or lower was higher than expected based on the distribution in an age and gender-matched manufacturer reference population, and that males are at a higher risk than females of having a BMD lumbar Z-score of less than -1.5 . The proportion of those with BMD Z-scores more than 1 SD above the mean in the reported study was not statistically significantly different from that expected in reference population.

Most bone mineral accrual occurs prior to age 14.0 ± 1.0 years in boys and 12.5 ± 0.9 years in girls[36], with 90% of peak bone mass attained before the age of 18 years [44]. It is possible that the older age at diagnosis (median, 15 years) of our HL survivor cohort, compared with the younger age of children treated for ALL, may have attenuated the potential effect of treatment. Our finding that males are at a significantly higher risk for BMD deficits than females is consistent with prior reports[9]. In contrast to females in our study being diagnosed with HL near the expected time of maturity (median, 16.2 years), the males were diagnosed about 2.1 years earlier (median, 14.1 years) corresponding to an expected period of rapid maturation and BMD accretion. Thus, the impact of treatment on bone mineral accretion may have been greater in males by interfering with hormonal stimulation.

Specific chemotherapeutic agents[9,16-18,45], cranial radiation[4,46,47], and hypogonadism[10] have been reported to be associated with BMD deficits in survivors of childhood cancer. Corticosteroids are particularly problematic[44]. Because nearly all of the patients in our cohort received prednisone (99.1%) in combination chemotherapy regimens, we were unable to assess the role of prednisone alone on BMD deficits. Additionally, the exposure of children and adolescents with HL to corticosteroids is time limited when compared to children with other cancers or chronic conditions[9,48]. In contrast, patients with HL treated with contemporary therapy have a relatively brief exposure to

glucocorticoids that does not typically exceed 2 to 3 months in duration. Recognition of the magnitude of BMD outcomes based on this difference in exposures is particularly pertinent. Our results suggest that brief exposure confers a relatively low risk of BMD deficit in survivors of pediatric HL many years after completion of therapy.

Methotrexate (MTX) has also been implicated in the development of BMD deficits [49]. However, in our study MTX was not a risk factor for low BMD, possibly because of the relatively low cumulative doses used.

Radiation-associated endocrinopathy impacting the hypothalamic-pituitary axis, thyroid gland and gonads may also have adverse effects on bone mineralization[9-12] as seen in survivors of childhood ALL and brain tumors [9,10,28]. However, the radiation therapy used to treat HL is directed toward nodal involvement, potentially including endocrine organs such as the thyroid and ovaries. An excess risk of both hypothyroidism and hyperthyroidism has been reported in HL survivors treated with cervical radiation[50]. While hyperthyroidism promotes bony demineralization, this condition is much less common than hypothyroidism; iatrogenic hyperthyroidism resulting from overzealous thyroid hormone replacement could predispose to BMD loss. Only 8 (12.3%) of 65 patients on thyroid hormone therapy reported here, had subnormal TSH levels consistent with over-treatment. However, the median BMD Z-score of these 8 patients (0.31, range -0.61 to 2.55) did not indicate an adverse impact of thyroid hormone therapy on BMD.

Gonadal dysfunction may result from radiation injury to the hypothalamic-pituitary-gonadal axis, and from treatment with alkylating agents like cyclophosphamide leading to decreased BMD[9]. However, we did not observe an association between BMD deficits of at least 1.5 SD below the mean and hypogonadism in this cohort of HL survivors. A possible explanation for this finding is that hormone replacement therapy prevented the potential alteration of BMD related to radiation- or chemotherapy-induced hormonal deficits. Further, none of the patients received radiation therapy to the hypothalamic-pituitary axis and thus, a central adverse effect of BMD was absent. Lastly, gonadotoxic therapy was limited to no or low cumulative doses of alkylating agents and, in a proportion, pelvic radiation (8 of 133; 6%). Thus, potential therapy-induced BMD deficits were generally minimized and developed in a small subset of male patients.

Our study is limited by its retrospective nature and small cohort size. While all patients had prospective assessment of growth, pubertal, menstrual and pregnancy history, prospective laboratory evaluation of gonadal function was limited to survivors exposed to potentially gonadotoxic therapy and those with a clinical indication for this testing. An accurate and complete fracture history for this cohort, would have been helpful to assess the potential clinical implications of BMD deficits. Further, we lacked information about genetic predisposition and lifestyle factors such as calcium intake, smoking, physical activity that contribute to BMD. In spite of these shortcomings, this report of BMD in childhood survivors of HL contributes to the understanding of this topic and may help in the future development of health screening guidelines for long-term HL survivors.

In summary, we found that long-term survivors of pediatric HL had negligible BMD deficits. Since the patients studied are at least 5 years from therapy, we can conclude that contemporary therapy for HL does not predispose the vast majority of survivors to long-term BMD deficits. However, the significantly increased risk of BMD deficits observed in male survivors warrants further study. Future investigations should examine the need for sequential follow up, because it is not known whether BMD deficits continue over the years, recover or reach a plateau and whether HL survivors with BMD deficits are at significant risk of fractures.

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Reference List

1. Ferrari S, Rizzoli R, Chevalley T, et al. Vitamin-D-receptor-gene polymorphisms and change in lumbar-spine bone mineral density. *Lancet*. 1995; 345:423–424. [PubMed: 7853953]
2. Sainz J, Van Tornout JM, Loro ML, et al. Vitamin D-receptor gene polymorphisms and bone density in prepubertal American girls of Mexican descent. *N Engl J Med*. 1997; 337:77–82. [PubMed: 9211676]
3. Howard G, Nguyen T, Morrison N, et al. Genetic influences on bone density: physiological correlates of vitamin D receptor gene alleles in premenopausal women. *J Clin Endocrinol Metab*. 1995; 80:2800–2805. [PubMed: 7673427]
4. Gilsanz V, Carlson ME, Roe TF, Ortega JA. Osteoporosis after cranial irradiation for acute lymphoblastic leukemia. *J Pediatr*. 1990; 117:238–244. [PubMed: 2116509]
5. Dacou-Voutetakis C, Xypolyta A, Haidas S, et al. Irradiation of the head. Immediate effect on growth hormone secretion in children. *J Clin Endocrinol Metab*. 1977; 44:791–794. [PubMed: 849990]
6. Shalet SM, Beardwell CG, Pearson D, Jones PH. The effect of varying doses of cerebral irradiation on growth hormone production in childhood. *Clin Endocrinol (Oxf)*. 1976; 5:287–290. [PubMed: 954222]
7. Lustig RH, Schriock EA, Kaplan SL, Grumbach MM. Effect of growth hormone-releasing factor on growth hormone release in children with radiation-induced growth hormone deficiency. *Pediatrics*. 1985; 76:274–279. [PubMed: 3927254]
8. Blatt J, Lee P, Suttner J, Finegold D. Pulsatile growth hormone secretion in children with acute lymphoblastic leukemia after 1800 cGy cranial radiation. *Int J Radiat Oncol Biol Phys*. 1988; 15:1001–1006. [PubMed: 3182308]
9. Kaste SC, Jones-Wallace D, Rose SR, et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. *Leukemia*. 2001; 15:728–734. [PubMed: 11368432]
10. Petraroli M, D'Alessio E, Ausili E, et al. Bone mineral density in survivors of childhood brain tumours. *Childs Nerv Syst*. 2007; 23:59–65. [PubMed: 17058089]
11. Nysom K, Holm K, Michaelsen KF, et al. Bone mass after treatment of malignant lymphoma in childhood. *Med Pediatr Oncol*. 2001; 37:518–524. [PubMed: 11745890]
12. Gilsanz V, Gibbens DT, Roe TF, et al. Vertebral bone density in children: effect of puberty. *Radiology*. 1988; 166:847–850. [PubMed: 3340782]
13. Arikoski P, Komulainen J, Voutilainen R, et al. Reduced bone mineral density in long-term survivors of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 1998; 20:234–240. [PubMed: 9628435]
14. Kaste SC. Bone-mineral density deficits from childhood cancer and its therapy. A review of at-risk patient cohorts and available imaging methods. *Pediatr Radiol*. 2004; 34:373–378. [PubMed: 14963622]
15. van der Sluis I, van den Heuvel-Eibrink MM. Osteoporosis in children with cancer. *Pediatr Blood Cancer*. 2008; 50:474–478. [PubMed: 18064660]
16. Kaste SC, Ahn H, Liu T, et al. Bone mineral density deficits in pediatric patients treated for sarcoma. *Pediatr Blood Cancer*. 2008; 50:1032–1038. [PubMed: 17570705]
17. Kelly J, Damron T, Grant W, et al. Cross-sectional study of bone mineral density in adult survivors of solid pediatric cancers. *J Pediatr Hematol Oncol*. 2005; 27:248–253. [PubMed: 15891558]

18. Wasilewski-Masker K, Kaste SC, Hudson MM, et al. Bone mineral density deficits in survivors of childhood cancer: long-term follow-up guidelines and review of the literature. *Pediatrics*. 2008; 121:e705–e713. [PubMed: 18310191]
19. Atkinson SA, Halton JM, Bradley C, et al. Bone and mineral abnormalities in childhood acute lymphoblastic leukemia: influence of disease, drugs and nutrition. *Int J Cancer Suppl*. 1998; 11:35–39. [PubMed: 9876475]
20. Weaver CM. The role of nutrition on optimizing peak bone mass. *Asia Pac J Clin Nutr*. 2008; 17(Suppl 1):135–137. [PubMed: 18296321]
21. Specker B, Vukovich M. Evidence for an interaction between exercise and nutrition for improved bone health during growth. *Med Sport Sci*. 2007; 51:50–63. [PubMed: 17505119]
22. Seibel MJ. Bone turnover in nutrition-related disorders. *Wien Med Wochenschr*. 2007; 157:582–588. [PubMed: 18204958]
23. Loud KJ, Gordon CM. Adolescent bone health. *Arch Pediatr Adolesc Med*. 2006; 160:1026–1032. [PubMed: 17018461]
24. Ondrak KS, Morgan DW. Physical activity, calcium intake and bone health in children and adolescents. *Sports Med*. 2007; 37:587–600. [PubMed: 17595154]
25. Eastell R. Role of oestrogen in the regulation of bone turnover at the menarche. *J Endocrinol*. 2005; 185:223–234. [PubMed: 15845915]
26. Vanderschueren D, Vandenput L, Boonen S. Reversing sex steroid deficiency and optimizing skeletal development in the adolescent with gonadal failure. *Endocr Dev*. 2005; 8:150–165. [PubMed: 15722623]
27. Rogol AD, Roemmich JN, Clark PA. Growth at puberty. *J Adolesc Health*. 2002; 31:192–200. [PubMed: 12470915]
28. Odame I, Duckworth J, Talsma D, et al. Osteopenia, physical activity and health-related quality of life in survivors of brain tumors treated in childhood. *Pediatr Blood Cancer*. 2006; 46:357–362. [PubMed: 16035080]
29. Holmes SJ, Whitehouse RW, Clark ST, et al. Reduced bone mineral density in men following chemotherapy for Hodgkin's disease. *Br J Cancer*. 1994; 70:371–375. [PubMed: 8054287]
30. El Ziny MA, Al Tonbary YA, Salama OS, et al. Low bone mass in children with malignant lymphoma. *Pediatr Hematol Oncol*. 2007; 24:577–585. [PubMed: 18092248]
31. van der Sluis I, van den Heuvel-Eibrink MM, Hahlen K, et al. Bone mineral density, body composition, and height in long-term survivors of acute lymphoblastic leukemia in childhood. *Med Pediatr Oncol*. 2000; 35:415–420. [PubMed: 11025472]
32. van der Sluis I, van den Heuvel-Eibrink MM, Hahlen K, et al. Altered bone mineral density and body composition, and increased fracture risk in childhood acute lymphoblastic leukemia. *J Pediatr*. 2002; 141:204–210. [PubMed: 12183715]
33. Sklar C, Boulad F, Small T, Kernan N. Endocrine complications of pediatric stem cell transplantation. *Front Biosci*. 2001; 6:G17–G22. [PubMed: 11487479]
34. Strauss AJ, Su JT, Dalton VM, et al. Bony morbidity in children treated for acute lymphoblastic leukemia. *J Clin Oncol*. 2001; 19:3066–3072. [PubMed: 11408503]
35. Kaste SC, Rai SN, Fleming K, et al. Changes in bone mineral density in survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2006; 46:77–87. [PubMed: 16106430]
36. Whiting SJ, Vatanparast H, Baxter-Jones A, et al. Factors that affect bone mineral accrual in the adolescent growth spurt. *J Nutr*. 2004; 134:696S–700S. [PubMed: 14988470]
37. Brennan BM, Mughal Z, Roberts SA, et al. Bone mineral density in childhood survivors of acute lymphoblastic leukemia treated without cranial irradiation. *J Clin Endocrinol Metab*. 2005; 90:689–694. [PubMed: 15562013]
38. Donaldson SS, Hudson MM, Lamborn KR, et al. VAMP and low-dose, involved-field radiation for children and adolescents with favorable, early-stage Hodgkin's disease: results of a prospective clinical trial. *J Clin Oncol*. 2002; 20:3081–3087. [PubMed: 12118021]
39. Hudson MM, Krasin M, Link MP, et al. Risk-adapted, combined-modality therapy with VAMP/COP and response-based, involved-field radiation for unfavorable pediatric Hodgkin's disease. *J Clin Oncol*. 2004; 22:4541–4550. [PubMed: 15542805]

40. Friedmann AM, Hudson MM, Weinstein HJ, et al. Treatment of unfavorable childhood Hodgkin's disease with VEPA and low-dose, involved-field radiation. *J Clin Oncol*. 2002; 20:3088–3094. [PubMed: 12118022]
41. Cann CE. Quantitative CT for determination of bone mineral density: a review. *Radiology*. 1988; 166:509–522. [PubMed: 3275985]
42. QCT PRO. Mindwaves Software. San Francisco, CA:
43. Agresti, A. Categorical data analysis. Wiley and Sons; New York: 2002.
44. Pagano-Therrien J, Santacroce SJ. Bone mineral density decrements and children diagnosed with cancer. *J Pediatr Oncol Nurs*. 2005; 22:328–338. [PubMed: 16216895]
45. van dS I, van den Heuvel-Eibrink MM. Osteoporosis in children with cancer. *Pediatr Blood Cancer*. 2008; 50:474–478. [PubMed: 18064660]
46. Kaste SC, Jones-Wallace D, Rose SR, et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. *Leukemia*. 2001; 15:728–734. [PubMed: 11368432]
47. Nysom K, Molgaard C, Holm K, et al. Bone mass and body composition after cessation of therapy for childhood cancer. *Int J Cancer Suppl*. 1998; 11:40–43. [PubMed: 9876476]
48. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med*. 2006; 354:166–178. [PubMed: 16407512]
49. Johnston A, Gudjonsson JE, Sigmundsdottir H, et al. The anti-inflammatory action of methotrexate is not mediated by lymphocyte apoptosis, but by the suppression of activation and adhesion molecules. *Clin Immunol*. 2005; 114:154–163. [PubMed: 15639649]
50. Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab*. 2000; 85:3227–3232. [PubMed: 10999813]

Figure 1.

Histogram showing no difference in distribution of bone mineral density Z-scores observed in study cohort compared to that expected in age- and sex-matched general population ($p=0.503$).

Table I**Clinical Characteristics of Eligible and Participating Hodgkin Lymphoma Survivors**

Characteristic	Total (n = 133)	With (n = 109)	Without (n = 24)	P value
Sex				0.003
Female (%)	58 (43.6%)	54 (49.5%)	4 (16.7%)	
Male (%)	75 (56.4%)	55 (50.5%)	20 (83.3%)	
Race				0.536 [†]
White (%)	112 (84.2%)	93 (85.3%)	19 (79.2%)	
Other (%)	21 (15.8%)	16 (14.7%)	5 (20.8%)	
Age at Diagnosis				0.545
Median(range)	15.4 (3.1 - 21.8)	15.1 (3.1 - 20.7)	16.1 (4.8 - 21.8)	
Mean±SD	14.6±3.9	14.6±3.9	15.0±4.1	
Years from Dx to LFU				0.097
Median(range)	9.4 (5.1 - 13.0)	9.5 (5.1 - 13.0)	8.0 (5.6 - 12.9)	
Mean±SD	9.0±1.9	9.2±1.8	8.5±2.1	
Histology				0.550
NS (%)	90 (67.7%)	75 (68.8%)	15 (62.5%)	
O (%)	43 (32.3%)	34 (31.2%)	9 (37.5%)	
Risk				0.319 [†]
Favorable (%)	44 (33.1%)	33 (30.3%)	11 (45.8%)	
Intermediate (%)	17 (12.8%)	15 (13.8%)	2 (8.3%)	
Unfavorable (%)	72 (54.1%)	61 (56.0%)	11 (45.8%)	
Hypothyroidism				0.048
Yes (%)	74 (55.6%)	65 (59.6%)	9 (37.5%)	
No (%)	59 (44.4%)	44 (40.4%)	15 (62.5%)	
Hypogonadism				0.462 [†]
Yes (%)	23 (17.3%)	19 (17.4%)	4 (16.7%)	
No (%)	67 (50.4%)	60 (55.0%)	7 (29.2%)	
Radiation to lumbar spine				0.634
Yes (%)	39 (29.3%)	31 (28.4%)	8 (33.3%)	
No (%)	94 (70.7%)	78 (71.6%)	16 (66.7%)	
Procarbazine				0.090
Yes (%)	80 (60.2%)	69 (63.3%)	11 (45.8%)	
No (%)	51 (38.3%)	38 (34.9%)	13 (54.2%)	
Cyclophosphamide				0.042
Yes (%)	85 (63.9%)	74 (67.9%)	11 (45.8%)	
No (%)	48 (36.1%)	35 (32.1%)	13 (54.2%)	
Methotrexate (mg/m²)				0.434
≤ 150 (%)	92 (69.2%)	77 (70.6%)	15 (62.5%)	
> 150 (%)	41 (30.8%)	32 (29.4%)	9 (37.5%)	
Prednisone (mg/m²)				0.740

Characteristic	Total (n = 133)	With (n = 109)	Without (n = 24)	P value
<= 2000 (%)	87 (65.4%)	72 (66.1%)	15 (62.5%)	
> 2000 (%)	46 (34.6%)	37 (33.9%)	9 (37.5%)	
Relapse				1.000 [†]
Yes (%)	6 (4.5%)	5 (4.6%)	1 (4.2%)	
No (%)	127 (95.5%)	104 (95.4%)	23 (95.8%)	

[†] P value from exact Chisq test

[#] Data regarding laboratory evaluation of gonadal function was available only for the 43 survivors at risk for gonadal dysfunction based on treatment including alkylating agent chemotherapy or radiation to fields potentially impacting the gonads and those clinically suspected of gonadal dysfunction also underwent such laboratory evaluation. All others were considered to have normal gonadal function based on pubertal progress and menstrual cycle function.

Table IIOdds Ratio Estimates of Bone Deficit ($Z \leq -1.5$) from Univariable and Multivariable Logistic Models

Factor	Univariable Model		Multivariable Model	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex				
Male vs. Female	3.49 (1.05–11.61)	0.042	3.58 (1.06–12.10)	0.040
Race				
White vs. Other	4.52 (0.70–Inf)	0.128		
BMI (kg/m²)				
Normal + Underweight vs. Overweight + Obesity	2.67 (0.86–8.30)	0.089	2.76 (0.87–8.76)	0.086
Years from diagnosis to QCT				
One-year increase	1.10 (0.83–1.45)	0.507		
Age at diagnosis				
One-year increase	0.98 (0.82–1.18)	0.845		
Age at QCT				
One-year increase	0.97 (0.85–1.10)	0.630		
Radiation to lumbar spine				
Yes vs. No	0.82 (0.18–3.01)	1.000		
Procarbazine				
Yes vs. No	1.25 (0.40–3.91)	0.700		
Cyclophosphamide				
Yes vs. No	1.05 (0.33–3.29)	0.936		
Methotrexate (mg/m²)				
>120 vs. ≤ 120	1.11 (0.28–3.88)	1.000		
Prednisone (mg/m²)				
> 1680 vs. ≤ 1680	1.15 (0.37–3.61)	0.805		