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Bone mineral density deficits and fractures in survivors of childhood cancer

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Abstract

Although substantial increases in survival rates among children diagnosed with cancer have been observed in recent decades, survivors are at risk of developing therapy-related chronic health conditions. Among children and adolescents treated for cancer, acquisition of peak bone mass may be compromised by cancer therapies, nutritional deficiencies and reduced physical activity. Accordingly, failure to accrue optimal bone mass during childhood may place survivors at increased risk for deficits in bone density and fracture in later life. Current recommendations for the treatment of bone density decrements among cancer survivors include dietary counseling and supplementation to ensure adequate calcium and vitamin D intake. Few strategies exist to prevent or treat bone loss. Moving forward, studies characterizing the trajectory of changes in bone density over time will facilitate the development of interventions and novel therapies aimed at minimizing bone loss among survivors of childhood cancer.

Keywords

Cancer; childhood; survivor; late effect; bone; osteoporosis; osteopenia; bone mineral density; glucocorticoid; methotrexate; cranial radiation; bisphosphonate

INTRODUCTION

Advances in treatment and hospital care for children diagnosed with cancer have resulted in an increasing population of childhood cancer survivors. Over 80% of children newly diagnosed with cancer will survive for at least five years after their initial diagnosis [1]. Unfortunately, cure is not without consequences. Adult survivors of childhood cancer are at risk for chronic conditions with 80.5% developing one or more severe, disabling or life

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threatening chronic condition by 45 years of age [2]. Chronic conditions observed in survivors of childhood cancer are diverse in nature and can include skeletal morbidity, such as low bone mineral density (BMD), avascular necrosis, and second malignant bone tumors [3–9]. In a recent report from the St. Jude Lifetime Cohort Study, among young adult survivors at a median age of 32 years, 9.6% of survivors exposed to therapies known to adversely affect bone metabolism were diagnosed with osteoporosis [2].

Bone strength is determined by both its structural characteristics (geometry and microarchitecture) and its material properties (collagen composition and mineral-to-matrix ratio) [10]. Because BMD accounts for approximately 60–70% of the variation, it is often used to indirectly characterize bone strength [11]. Differences in bone density are determined early in life. Bone mass increases throughout childhood and adolescence; peak bone mass is achieved between 20 and 30 years of age [12]. Subsequently, there is a gradual age-related decline that accelerates in later life. Substantial bone loss in aging adults can result in osteoporosis, a systemic skeletal problem that predisposes individuals to fracture [13]. Although osteoporosis is a disease that primarily affects the elderly, it has its foundation in childhood; the amount of bone accrued in childhood modifies the impact of bone loss in later adulthood [12]. Children and adolescents diagnosed with cancer are at risk of developing deficits in bone density as a result of disturbances in normal bone accretion and metabolism [14,15]. Among children with cancer, acquisition of peak bone mass may be adversely effected by cancer therapies, nutritional deficiencies and reduced physical activity [16,17]. In children diagnosed with acute lymphoblastic leukemia (ALL), bone density may be directly affected by the leukemic process. Failure to accrue sufficient bone mass during childhood may place childhood cancer survivors at an increased risk for fracture and osteoporosis later in life.

PREVALENCE OF BMD DEFICITS AND FRACTURES AMONG SURVIVORS

Deficits in BMD among individuals diagnosed with childhood cancer have been well-documented [5–9]. Among children newly diagnosed with ALL, between 13% and 21% will present with decrements in BMD [6,9]. Children with ALL may also present with bone pain and fractures, as well as with radiographic evidence of metaphyseal lucencies, lytic and sclerotic lesions, and periosteal elevations [8]. During treatment, bone density decreases relative to initial levels observed at diagnosis [6,7,9,15]. Some investigators have suggested that BMD may improve in the years immediately following the completion of therapy, as mean lumbar spine and total body Z-scores among ALL survivors have not consistently been observed to differ significantly from normative values [9,18–20]. However, other investigators have reported significant decrements in BMD among ALL survivors 20 or more years from treatment (Table 1) [14,17,21–24].

Although the majority of bone density studies among children newly diagnosed with cancer have been conducted in ALL populations, in a study of neuroblastoma, 26% of children demonstrated lumbar spine BMD Z-scores less than -2.0 at diagnosis [25]. Among long-term survivors of non-hematological cancers, previous studies have indicated that up to 41% of Hodgkin lymphoma survivors [26], 43% of intracranial germ cell tumor survivors [27], 47% of survivors of brain tumors, and 50% of non-Hodgkin lymphoma survivors [26] will

exhibit deficits in BMD (Table 1). A high prevalence of BMD deficits have also been reported among survivors of bone tumors. Holzer et al reported BMD deficits (Z-score < -1) in lumbar spines or proximal femurs in 65% of long-term survivors of osteosarcoma assessed an average of 16 years from cancer diagnosis [28].

An increased frequency of fracture has also been reported in children and adolescents diagnosed with cancer [9,15,29,30]. In a study of 186 children with ALL screened using radiography within 30 days of diagnosis, 16% of children were found to have one or more vertebral compression fracture [29]. The distribution of fractures was bimodal, with most occurring in midthoracic (T6/T7) and thoracolumbar (T12-L2) regions. The location of the fractures was suggested to reflect the regions where mechanical stress on the vertebrae is greatest [29,31]. The authors also noted that for every one standard deviation reduction in BMD z-score of the lumbar spine, the odds for fracture increased by 80% (95%CI=10–193%)[29]. A high prevalence of fracture is also reported during treatment for ALL, with up to 39% of participants incurring one or more fractures [15]. In a study by Hogler et al, the five-year cumulative incidence of fractures from diagnosis of ALL was 13.5% [30]. Other studies have estimated that the fracture rate among children being treated for cancer is 6-fold higher than expected [9]. Although the increased risk for fracture among children being treated for cancer may reflect bone mineral loss during therapy, low BMD has not been consistently associated with an increased likelihood of fracture across all studies [9,32]. The occurrence of fracture among long-term survivors remains largely uncharacterized. In a report from the Childhood Cancer Survivor Study 7414 cancer survivors of mixed diagnoses were followed for a median of 22 years, the prevalence of self-reported fractures were not found to be significantly higher than that observed among 2374 siblings [33].

TREATMENT-RELATED RISK FACTORS FOR BMD DEFICITS

Corticosteroid administration is essential for cure among children with ALL, and also used in the treatment of other childhood cancers including Hodgkin and non-Hodgkin lymphoma. Corticosteroids are also used as prophylaxis for graft versus host disease (GVHD) in patients following hematopoietic stem cell transplant (HSCT). Prolonged use of corticosteroids has been demonstrated to adversely affect bone metabolism by altering the balance between bone resorption and formation, by increasing the life-span of osteoclasts, and by reducing osteoblast activity and differentiation [7,34–36]. Normal bone metabolism may be further compromised by steroid-induced alterations in calcium homeostasis and reduced muscle strength, or by interfering with function of the growth hormone/insulin-like growth factor 1 (IGF-1) axis [35]. Children treated with prednisone equivalent corticosteroid doses in excess of 9000 mg/m² are at risk for deficits in BMD during treatment that persist into adulthood [19]. Type of corticosteroid may also be of clinical importance, as a higher incidence of fractures and osteonecrosis has been observed among ALL patients treated with dexamethasone during post-remission therapy when compared to regimens incorporating prednisone alone [36].

Methotrexate (MTX), an anti-folate agonist, exerts its cytotoxic action by reversibly inhibiting the enzyme dihydrofolate-reductase (DHFR) [37]. Dihydrofolate-reductase catalyzes the conversion of dihydrofolate to tetrahydrofolate, limiting the production of

thymidine and purine bases, and thereby impairing DNA and RNA synthesis. Methotrexate-induced osteopathy has been reported in infants with brain tumors [38], and in children receiving high-dose therapy for osteosarcoma [39]. In addition, children with methotrexate-induced osteopathy may present with bone pain and fractures [8]. Methotrexate is associated with reduced proliferation of pre-osteoblasts and osteoblasts [40], simultaneously increasing osteoclast formation in the bone marrow, and elevating osteoclast density on bone surface [41]. Furthermore, methotrexate is nephrotoxic and alters calcium metabolism, resulting in hypomagnesaemia, which affects bone formation [42]. Higher doses of glucocorticoids and MTX ($>40,000$ mg/m²) in children with ALL are associated with severe bone loss that fails to recover after chemotherapy completion [19,28].

Radiation is known to damage the microvasculature within bone and its surrounding tissue, and has a direct cytotoxic effect on epiphyseal chondrocytes [42]. Consequently, direct irradiation to bone can lead to localized osteopenia, and other skeletal sequelae including retarded bone growth, reduced sitting height and kyphoscoliosis [43,44]. The long-term effects of irradiation on bone are more pronounced at doses exceeding 20 Gy, or when radiation takes place at a younger age [45]. Radiation-induced osteopenia and fractures have been reported to occur within the field of prior radiation [46–48]. In some instances, the occurrence of such fractures will lead to a subsequent diagnosis of a recurrence of the childhood tumor or a second primary malignancy [46–48]. In contrast, among patients receiving total body irradiation (TBI) in preparation for HSCT, reduction in BMD of the lumbar spine has not been observed [49].

Therapy related endocrinopathies can also increase the risk of BMD deficits among survivors of childhood cancer. Previous studies have reported an increased incidence of low BMD in survivors of childhood cancer treated with cranial radiation (CRT) [14,50]. The association between CRT and bone mineralization is likely a consequence of damage to the hypothalamic-pituitary axis, reducing growth hormone (GH) secretion. Growth hormone promotes bone formation, either directly or via IGF-I, stimulating the proliferation and activity of osteoblasts [51]. Moreover, GH can directly influence growth by promoting proliferation and differentiation of chondrocytes within the epiphyseal growth plates. The incidence of GH deficiency among survivors is directly related to the pituitary radiation dose and inversely related to age at radiation exposure [52,53]. Although several studies have reported an increased risk of BMD deficits among survivors with GH deficiency or who were treated with cranial irradiation, [21,23,54,55] interpretation of these findings has been complicated by the association between GH deficiency and short adult stature [56]. Bone size and mass vary according to height, such that short people generally have smaller bones. DXA calculations of BMD are based on an areal measurement (g/cm²) that does not consider the thickness of the bone, thereby underestimating BMD among children and adults of short stature [56]. Nevertheless, findings from a study of survivors of mixed cancer diagnoses, using QCT to determine BMD of the lumbar spine, demonstrated a 3.6-fold increased risk among survivors exposed to 24 Gy of CRT when compared to those treated with 18 Gy or no radiation (95% CI=1.1–12.0; $p=0.016$) [57]. Unfortunately, a study of ALL survivors treated with five years of GH replacement therapy reported no beneficial effect for BMD [58].

Hypogonadism influences BMD in both males and females [59]. Among survivors of childhood cancer, hypogonadism may be the result of direct damage to the ovaries and the testes from pelvic radiation or alkylating agents, or the result of gonadotropin deficiency following CRT. Among male survivors, frank Leydig cell failure and androgen insufficiency are relatively uncommon following chemotherapy without radiation [60,61]. However, subclinical dysfunction, represented by elevated levels of luteinizing hormones has been reported among 10–57% of recipients receiving standard chemotherapy regimens [62,63]. Leydig cell failure is common among adolescent males exposed to testicular radiation doses in excess of 20 Gy [60]. While most females treated with standard chemotherapy will maintain or recover ovarian function [64,65], females receiving myeloablative treatment for HSCT, which may include busulfan, melphalen and thiotepea, are at high risk of hypogonadism [66]. Radiation induced hypogonadism in females is affected by age at exposure. Approximately 50% of prepubertal girls who receive 10 Gy of fractionated TBI will enter puberty spontaneously, whereas almost all females who are 10 or more years of age will experience ovarian failure [67,68]. The incidence of gonadotropin deficiency is highest in survivors who receive direct irradiation to the pituitary gland, occurring at doses of greater than 20 Gy [69]. Estrogen replacement may negate the loss of sex hormones and reduce the risk of low BMD among female survivors [70,71], although findings are not consistent across all studies [59]. Limited data exists examining the influence of androgen insufficiency on BMD in male survivors of childhood cancer [72].

ADDITIONAL RISK FACTORS FOR BMD DEFICITS

Due to the high number of children with ALL who present with BMD decrements at diagnosis, poor mineralization among ALL patients may be associated with the leukemic process. Direct infiltration of leukaemic cells into bone and expansion within the medullary cavity may damage spongiosa, and can cause bone pain in children with ALL [73]. Bone metabolism may be compromised by factors secreted by leukemic cells such as osteoblast-inhibiting factor, prostaglandin E and parathyroid hormone-related peptide [73]. At diagnosis, markers of bone formation, such as procollagen type I, C-terminal propeptide and bone alkaline phosphatase, are reduced, [9,74,75] while markers of bone resorption, including bone collagen degradation peptide and carboxyterminal telopeptide of type I collagen, may be reduced or normal [9,74,75]. These studies suggest an overall decrease in bone turnover among newly diagnosed patients, which may contribute to BMD decrements.

Children and adolescents diagnosed with cancer are at risk of deficits in BMD as a result of the side effects of having a chronic condition, such as nutritional deficiencies and reduced physical activity levels [16,17]. Children require sufficient calories as well as adequate calcium and vitamin D intake to provide the energy and mineral necessary for bone growth [76]. Chemotherapy can cause nausea or vomiting; alternatively, children receiving large doses of steroids may exhibit voracious appetites. Low dietary intakes of calcium and vitamin D have been reported among survivors of CNS tumors who also had significant BMD deficits [77]. Low physical activity levels both during and after treatment for childhood cancer can contribute to cardiac deconditioning and skeletal muscle atrophy [78]. As muscle force induces bone adaptation [79], reduced muscle mass may exacerbate bone loss in children treated for cancer. Physical activity levels and fitness are positively

associated with increased lumbar spine Z-scores among survivors of CNS tumors [80] and Wilms tumor [81]. Furthermore, exercise capacity has been associated with bone mineral content at the hip among survivors of ALL [17].

Cancer treatment during adolescence and male sex are associated with increased risks for low BMD among ALL survivors [21,24,36,57]. Because bone mineral accretion accelerates during puberty, it is reasonable to expect that disturbances in bone metabolism during adolescence may have a large impact on peak bone mass [36]. Although it is not known why the prevalence and severity of BMD deficits are higher among male survivors, [21,36,57] studies suggest males may be more sensitive to the effects of glucocorticoids [82].

Although data are limited, a small number of studies exist which suggest that naturally-occurring genetic variation may influence bone density in children diagnosed with cancer. In children newly diagnosed with ALL, variation in genes involved in folate metabolism, methylenetetrahydrofolate reductase and methionine synthase reductase, have been shown to influence BMD at diagnosis [83]. Among ALL survivors, a polymorphism in the corticotrophin-releasing hormone receptor-1 gene has been associated with reduced density of the trabecular lumbar spine among males [84]. In time, findings from genetic studies may facilitate identification of biological pathways that underlie skeletal morbidity in children with cancer, and may assist in the development of screening strategies for survivors at high-risk of these late effects. However, replication and extensive characterisation of genetic associations are required before such findings can influence clinical care.

SCREENING RECOMMENDATIONS

Clinical practice guidelines addressing screening and management of late effects among childhood cancer survivors have been independently developed by several cooperative groups and institutions. Early detection of treatment-related morbidity is critical for initiating interventions among childhood cancer survivors that may preserve health and improve quality of life. Screening recommendations from the Children's Oncology Group (COG) in the United States advise that survivors previously treated with therapies associated with low bone density should undergo baseline evaluation of BMD, by QCT or DXA, at entry into a long-term follow-up program [85]. An evaluation of BMD should also be considered for survivors with endocrinopathies known to influence bone density. The COG Long-Term Follow-Up (LTFU) guidelines (www-survivorshipguidelines.org) recommend a daily intake of 400 IU of vitamin D. Weight bearing exercise is also recommended.

PREVENTION AND TREATMENT

The high prevalence of bone density deficits among survivors of childhood cancer indicates that early identification and treatment, as well as interventions to improve bone density or delay bone loss, may be beneficial for a large number of survivors. Currently, treatments for BMD deficits among childhood cancer survivors include dietary counseling and supplementation to ensure adequate calcium and vitamin D intake [85]. Vitamin D and calcium supplementation has demonstrated efficacy in children with decrements in BMD following diagnosis of juvenile rheumatoid arthritis [86], idiopathic juvenile osteoporosis [87] and osteogenesis imperfect [88]. Early identification and treatment of conditions that

may exacerbate or accelerate bone loss, such as hypogonadism and GH deficiency, are also important in children or adolescents being treated for cancer [85]. In addition, it is important to recognize that while many late effects of therapy may arise during treatment or shortly thereafter, in many instances, some late effects may be absent or subclinical at the end of therapy, manifesting in later life. In a report from the St. Jude Lifetime Cohort Study, 1713 long-term survivors of mixed cancer types a median of 25 years from diagnosis were systematically screened according to the COG guidelines by medical assessment [2]. Among those survivors treated with therapies known to adversely affect endocrine organs, 11.8% of the females had primary ovarian failure, 11.5% of males had Leydig cell failure, and 56.4% had a disorder affecting the hypothalamic-pituitary axis. Of note, for more than 50% of survivors identified with Leydig cell failure or hypothalamic-pituitary disorders, the presence of these conditions was previously undiagnosed.

Pharmacologic interventions are available for individuals with severe BMD deficits or a history of multiple fractures. Bisphosphonates, which include alendronate and pamidronate, are agents that inhibit osteoclast-mediated bone resorption and are used in the treatment of primary and secondary osteoporosis [89]. Although bisphosphonates have not been tested in large groups of childhood cancer survivors for safety and efficacy, several small studies ($n < 20$) in children with ALL have shown that alendronate and pamidronate administered during and after the completion of chemotherapy can improve whole body BMD as well as markers of bone turnover [90–93]. Minimal side effects, such as fever and flu-like symptoms, were reported [92]. As bisphosphonates work by binding to calcium in the hydroxyapatite crystals of areas undergoing active remodeling, their half-life in bone may be several years depending on the rate of bone remodeling [89]. Thus, concerns regarding the potential for long-term effects of these agents in children have been raised, including impaired mineralization of bone, impaired linear growth, delayed bone healing following orthopedic procedures, and nephrocalcinosis [90–93]. So far, little published data exists supporting the occurrence of these adverse events in children. Nevertheless, children receiving bisphosphonates should be monitored by a qualified endocrinologist [85].

Joyce et al reported an association between upper body bone strength and BMD among young adult (mean age 35 years) survivors of childhood ALL, suggesting that interventions targeted to building lean muscle mass may be an approach toward improving bone mass in this population [94]. Many survivors of childhood cancer do not engage in regular exercise; [95] some studies report that less than 50% of cancer survivors meet recommended guidelines for physical activity [96]. There have been several studies in children in the maintenance phase of ALL, who have undergone resistance training intervention program for 8–12 weeks [97,98]. They were successful in improving muscle strength. A study by Hartman et al conducted a two year exercise intervention among children receiving therapy for ALL, but observed no improvement in BMD or muscle strength [99]. However, compliance to the intervention among patients in this study was low. Exercise interventions to improve bone health among adolescent or adult survivors of childhood cancer with persistent low BMD have not been evaluated.

RECOMMENDATIONS FOR FUTURE RESEARCH

Longitudinal studies of bone density, bone quality and fracture in children and adolescents treated for cancer are lacking. Although there are several longitudinal studies of children receiving treatment for ALL [6,7,9,15], most studies in long-term survivors are cross-sectional [7,17,19–22,24,26] and the incidence of BMD deficits and fractures are poorly characterized among patients with non-hematological cancers [33]. As a result, it is difficult to assess the significance of factors such as physical activity, nutrition, hormonal deficiencies, other chronic health conditions, and the natural aging process on the incidence of low bone density and fractures among childhood cancer survivors. Moreover, few strategies exist to prevent or treat bone loss. Moving forward, longitudinal studies that characterize the degree and trajectory of changes in bone density and tissue quality over time will facilitate identification of critical factors that potentiate bone loss among cancer survivors with aging. An improved understanding of the relative contribution of treatment, lifestyle and genetic factors on the risk of BMD deficits and fractures in cancer survivors may assist the development of intervention programs and novel therapies aimed at maximizing peak bone acquisition in childhood and adolescence and ameliorating bone loss in adulthood.

Therapies targeting childhood cancers continue to change over time with the introduction of new or modified chemotherapeutic protocols, and radiation oncology techniques [100]. For example, historically, CRT was the principle means of prophylaxis to prevent CNS relapse among children with ALL. However, recognition of the long-term endocrine and neurological complications associated with CRT resulted in a shift to treatment regimens that use glucocorticoids and intrathecal methotrexate for CNS prophylaxis. Thus, there will be an ongoing need to systematically follow cancer survivors treated using newer regimens to identify changes in the pattern of long-term skeletal morbidity [100].

CONCLUSIONS

Although a child with cancer may be cured, the effects of treatment are life-long, with findings from many studies indicating that survivors of childhood cancer are at risk of low bone density. The prevalence and severity of bone density deficits observed in survivors of childhood cancer is likely to increase over time as lifestyle factors, genetic predisposition, and the natural aging process modify the impact of previous cancer treatments on bone health. Hence, longitudinal studies characterizing the natural history of, and risk factors for, BMD deficits among childhood cancer survivors are warranted. Identification of high-risk groups may improve existing screening guidelines and facilitate the design and implementation of interventions directed at improving bone health, thereby, minimizing the risk fracture and osteoporosis in later life.

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Table 1

Prevalence of BMD deficits among survivors of childhood cancer

Cancer Diagnosis	Sample Size	Mean Age Diagnosis (years)	Mean Age Follow- up (years)	Method	Site	Mean Z-score	% low BMD (Z < -1)	% very low BMD (Z < -2)	Risk factors associated BMD deficits	Ref.
ALL	95	4.0 ^a	16.2 ^a	DXA	LS	-0.55				[14]
					TB	-0.39				
Mixed	60	6.3	12.4	DXA	LS	-0.28		8%	Decreased weight, height, and calcium intake	[7]
ALL	75 ^b	6.8	NA	DXA	TB	0.22	11%	0%	Less time since completion of maintenance therapy	[18]
ALL	106	5.8	15.9	DXA	LS	0.02	22%		High cumulative methotrexate and corticosteroid doses	[19]
ALL	23	5.4	17.2	DXA	LS	0.33		4%	Low calcium intake	[20]
					TB	0.19				
					LS ^c	0.12				
ALL	29	6.9 ^a male 6.8 ^a female	16.6 ^a male 17.6 ^a female	DXA	NA	NA			Male gender, CRT	[21]
ALL	31	6.9 ^a	23.0 ^a	QCT	LS ^d	-1.25 ^a				[22]
				DXA	LS	-0.74 ^a				
				SXA	FN	-0.43 ^a				
				DR	DR	-1.35 ^a				
ALL	24	6.8 male 9.9 female	23.4 male 27.4 female	DXA	FN	-1.07		45.8%	Impaired growth hormone secretion	[23]
					FT	-0.55				
					LS	-1.07				
					DR	-1.76				
					UD	-1.44				
HD	22	14.7	24.1	DXA	LS	-0.55 HD	41% HD		High corticosteroid dose	[26]

Cancer Diagnosis	Sample Size	Mean Age Diagnosis (years)	Mean Age Follow- up (years)	Method	Site	Mean Z-score	% low BMD ($Z < -1$)	% very low BMD ($Z < -2$)	Risk factors associated BMD deficits	Ref.
NHL	20	6.1	14.1		LS	-0.83 NHL	50% NHL			
GCT	28	11.5	23.1	DXA	LS ^d	-1.1	67.9%	25.0%	Male gender, Low lean mass	[27]
					FN	-0.4				
					TB	-0.8				
OS	48	NA	31.0	DXA	LS	-0.49	64.5% ^e	20.8% ^f		[28]
					FN	-0.90				
					TB	-0.47				
Mixed	97	4.5 ^a	14.3 ^a	DXA			45.4%	13.4%	Increasing CRT dose	[50]
Mixed	26	8 ^a	23 ^a	DXA	LS	-1.30 ^a			CRT, Pituitary insufficiency	[54]
					FN	-1.04 ^a				
ALL	141	4.0 ^a	15.9 ^a	QCT	LS	-0.78			Male gender, Caucasian, CRT	[57]
Mixed	40	12.7	25.8	SXA	DR	-1.57			Gonadal dysfunction	[59]
				DXA	FN	-0.68				
					TB	-0.33				
					LS	-0.22				
Brain tumor	24	6.7	12.1	DXA	TB	-0.47			Low calcium intake, Male gender	[77]
					LS	-1.27				
Brain tumor	25	8.5	15.6	DXA	TB	-0.91	44%	20%		[80]
					LS	-1.01				
Wilms tumor	31	3.6	13.7	DXA	TB	0.28	23.4%	16.1% ^g	Low levels of physical activity	[81]
					LS	-0.25				

ALL, acute lymphoblastic leukemia; CRT, cranial radiation; DR, 1/3 distal radius; DXA, dual X-ray absorptiometry; FN, femoral neck; GCT, intracranial germ cell tumor; HL, Hodgkins lymphoma; LS, lumbar spine; NHL, NA, not available; Non-Hodgkins lymphoma; OS, osteosarcoma; QCT, quantitative computed tomography; Ref., reference; SXA, single X-ray absorptiometry; TB, total body; UD, ultradistal.

^aMedian

- ^b Only 69% of participants had completed ALL therapy at BMD evaluation
- ^c Bone mineral apparent density was calculated to correct for bone size
- ^d Lumbar spine trabecular BMD
- ^e Proportion of survivors with a T-score below -1
- ^f Proportion of survivors with a T-score below -2.5
- ^g Proportion of survivors with a Z-score below -2.5