

Bone Mineral Density in Young Adult Survivors of Acute Lymphoblastic Leukemia

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BACKGROUND. The purpose of the current study was to determine the prevalence of low bone mineral density (BMD) (ie, osteopenia) and identify factors associated with low BMD in young adult survivors of childhood acute lymphoblastic leukemia (ALL).

METHODS. Dual energy x-ray absorptiometry was used to evaluate BMD in 74 randomly selected, long-term childhood ALL survivors initially treated in Minneapolis/St. Paul, Minnesota. Growth hormone (GH)-releasing hormone-arginine stimulation testing was conducted to evaluate peak GH level, and insulin-like growth factor I (IGF-I) and other markers of endocrine functioning were also evaluated in relation to BMD.

RESULTS. The mean age at the time of interview was 30 years, and the mean time since diagnosis was 24 years. Low BMD (Z-score, ≤ -1) was present in 24% of subjects, including 1 with osteoporosis. Low BMD was substantially more prevalent in men than in women and was strongly associated with short height. The mean height Z-score for those with low BMD was -1.44 , compared with a height Z-score of -0.39 ($P < .01$) for those with normal BMD. GH insufficiency, low IGF-I Z-score, and current smoking were also suggestive risk factors for low BMD.

CONCLUSIONS. In this long-term follow-up study of childhood ALL survivors, low BMD was found to be more prevalent than expected based on population normative data, specifically in men. The health consequences of early-onset BMD problems in childhood ALL survivors need to be carefully monitored. *Cancer* 2008;113:3248-56. © 2008 American Cancer Society.

KEYWORDS: adverse treatment effects, metabolic bone diseases, neoplasms, survivorship.

There are many known risk factors for low bone mineral density (BMD) and its associated morbidity in adults. These include advancing age, sedentary lifestyle, low calcium intake, vitamin D deficiency, hyperparathyroidism, smoking, white or Asian race, and onset of menopause.¹ Childhood acute lymphoblastic leukemia (ALL), the most common pediatric malignancy,² is also a potential risk factor for low BMD among adults who survive their disease and its treatment.³⁻⁷ The ALL disease process may alter bone mineralization, as evidenced by a high proportion of children with ALL found to have low 1,25(OH)₂D₃ and osteocalcin levels or hypercalciuria at diagnosis.^{4,8} In addition, high-dose glucocorticoids and intrathecal methotrexate, included in nearly all ALL treatment regimens, can affect bone formation, at least temporarily, by altering osteoblastic activity and proliferation.^{3,7,9-13} Many current adult survivors of ALL were treated with cranial radiation, which also affects bone growth and repair. Radiation-associated damage to the hypothalamic-pituitary axis can result in growth hormone (GH) deficiency and hypogo-

nadotropic/hypergonadotropic hypogonadism.^{5,14-19} Long-term endocrine abnormalities affect bone growth during childhood and the process of bone turnover and repair necessary for bone maintenance during adult life. Finally, the suboptimal activity and nutrition that these children face during their 2-year to 3-year treatment course are likely to reduce optimal bone formation during developmentally critical time periods.^{12,20}

The possibility that adult GH status among survivors of childhood ALL may be important to long-term bone health is of particular interest. Both GH and its byproduct, insulin-like growth factor I (IGF-I), are important regulators of the longitudinal growth of bone, and the process by which adult bone is maintained.^{21,22} GH and IGF-I appear to directly stimulate the proliferation and function of osteoblasts and chondrocytes.²² Chen et al performed hypophysectomies in rats and, even after replacing thyroid and glucocorticoid hormones, found decreased bone volume, trabecular number, and trabecular thickness.²³ In another study, the same group of authors added GH to the replacement regimen after the hypophysectomies, preventing loss in cortical and cancellous bone.²⁴

Low BMD is prevalent in individuals with either childhood-onset or adult-onset GH deficiency (GHD), and is particularly problematic for those individuals whose GHD onset occurred when they were children.^{25,26} Replacement during childhood does not completely alleviate the problem. Even children with GHD who were treated optimally with GH until they reached final adult height had BMD values 0.5 standard deviations (SD) below age-matched means as adults.²⁷ This may be because bone mass continues to accrue until the late 20s or early 30s.²² Although to our knowledge the impact of low BMD during early adulthood on long-term morbidity is not yet known, it appears possible that an early uncompensated BMD deficit may increase an individual's risk for early fracture,²⁷ long before it is expected with natural aging.

In a previous evaluation completed by our group, we reported that 64% of young adult survivors of childhood ALL had either insufficient or deficient responses to GH stimulation testing.²⁸ Because we also measured BMD in these individuals, and because our participants had a mean age of 30 years—the age range at which accrual of bone mass is believed to cease—we had a unique opportunity to also examine the association between GHD and BMD in this cohort. The primary objective of this analysis was to determine the prevalence of reduced BMD in young adult survivors of childhood ALL. The

second aim was to establish whether BMD deficits were associated with ALL treatment factors, including cranial radiation, or treatment-related factors such as GH deficiency or insufficiency. Because IGF-I is important in bone formation and repair, we also examined whether reduced IGF-I levels were associated with lower BMD.

MATERIALS AND METHODS

As described in greater detail previously,²⁸ we recruited 75 active participants from the Childhood Cancer Survivor Study²⁹ who were treated for ALL at either the University of Minnesota Children's Hospital or Children's Hospitals and Clinics of Minneapolis/St. Paul, Minnesota and diagnosed before age 21 years. From 207 eligible ALL survivors, potential subjects were stratified by past cranial radiation treatment (no cranial radiation, <24 grays [Gy], and ≥ 24 Gy), and 25 subjects from each treatment group were recruited using a block randomization sampling scheme designed to minimize the potential for favoring inclusion of "fast responders." Twenty-nine (14%) subjects actively or passively refused, 22 (10.6%) were lost to follow-up, 10 (4.8%) agreed to participate but were never scheduled because accrual in their block was met, and 71 (34.3%) were never contacted because their random number was not reached in our sampling scheme before the final recruitment sample size of 75 was reached. Written informed consent was obtained for each subject as approved by the human subjects review committees at the participating hospitals.

Biochemical tests were conducted in the fasting state at the General Clinical Research Center at the University of Minnesota. The GH-releasing hormone with arginine stimulation test (GHRH/ARG) for measuring peak GH secretion^{30,31} was completed for 72 of the 75 participants. GH-releasing hormone was administered at 1 $\mu\text{g}/\text{kg}$ as an intravenous bolus followed immediately by an intravenous infusion of arginine HCL (0.5 g/kg, maximum 30 g) given over 30 minutes. GH levels were obtained at 30 minutes, 40 minutes, 60 minutes, 90 minutes, and 120 minutes after completion of the arginine infusion. Consistent with previous studies using the GHRH/ARG stimulation test,^{31,32} peak GH level was categorized into 3 qualitative categories: normal GH, $>16.5 \mu\text{g}/\text{L}$; GH insufficient, 9 to 16.5 $\mu\text{g}/\text{L}$; and GH deficient, $<9 \mu\text{g}/\text{L}$. Insulin, IGF-I, thyroxine, and thyroid-stimulating hormone were measured with chemiluminescent immunoassays.³³ Three subjects had missing data for IGF-I (not the same 3 subjects with a missing GH study). The chemiluminescent immunoassays for

IGF-I were performed at ARUP Laboratories. Standardized IGF-I Z-scores were calculated based on the participant's age and sex according to the method described by Brabant³⁴ and used by ARUP Laboratories.³⁵ This method uses a cutoff of <2 SD below the predicted mean based on a mathematic modeling method to define abnormally low IGF-I.³⁴ The cutoff values for low IGF-I using this method are considerably lower than other published standards, such as Esoterix.³⁶

BMD was measured by dual-energy x-ray absorptiometry (DXA) (Prodigy software [version 6.7]; GE Lunar, Madison, Wis), which provided Z-scores standardized to sex, age, weight, and race/ethnicity for femoral neck, lumbar spine (L2-L4), and total body. Leukemia treatment data were abstracted from medical records as part of the Childhood Cancer Survivor Study.²⁹ The official position of the International Society for Clinical Densitometry states that the World Health Organization classifications (T-scores) for osteoporosis and osteopenia are not applicable to premenopausal women or to men, and recommended instead that Z-scores be used.³⁷ Therefore, using the lowest Z-score of the femoral neck, lumbar region, or total body, we defined low BMD as a Z-score ≤ -1 , and osteoporosis as a Z-score ≤ -2.5 , compared with individuals of the same sex, age, weight, and race, at ≥ 1 of the 3 measures.

Published data from the National Health and Nutrition Examination Survey (NHANES) were used to define age-specific and sex-specific normative values for height in non-Hispanic white Americans³⁸; from these data, a height Z-score was calculated for each study participant. The frequencies and proportions of low BMD were calculated across categorical variables and compared using the chi-square or Fisher exact tests. Unadjusted odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were estimated from logistic regression models. Differences in continuous variables were analyzed using the Student *t* test. Pearson correlation analyses were used to estimate linear associations between variables.

RESULTS

We previously showed that there were no statistically significant differences between the 75 subjects in the study and the remaining cohort of 132 ALL survivors presumed eligible to participate, according to sex, age at time of diagnosis or interview, body mass index (BMI), years of survival, or chemotherapies received.²⁸

One male subject was too large to fit in the DXA machine and was not included in this analysis. Table 1 shows mean values, stratified by sex and low BMD status, for clinical variables among the 74 subjects who underwent a DXA scan. The mean age at the time of the interview was 30 years, and the mean time since diagnosis was 24 years. Neither time factor differed by sex. Male ALL survivors in the study were considerably shorter on average than same-age white men based on NHANES population norms (mean height Z-score = -1.06), with only a minor difference in average height noted among female subjects compared with female population norms (mean Z-score = -0.35). Male subjects also had a lower mean peak GH level (18.5 $\mu\text{g/L}$) than did female subjects (34.8 $\mu\text{g/L}$) ($P = .06$). Overall, 18 (24%) subjects had a BMD that was ≥ 1 SD below the mean, including 1 whose BMD was ≤ -2.5 SD.

The mean height Z-score was the only characteristic or biologic value that statistically differed at a type I error probability of 5% between those with versus those without low BMD. The mean height Z-score was -1.44 for subjects with low BMD compared with -0.39 ($P < .01$) for those without low BMD. The Z-scores for BMD by femoral neck, L2-L4 lumbar spine, and total body are also shown in Table 1. Matched by sex, age, weight, and race/ethnicity, the lowest mean BMD Z-score for those with low BMD was in the lumbar spine (-1.12), and the mean Z-score for the lowest of the 3 site scores was -1.44 .

The distribution of selected demographic and clinical characteristics is presented in Table 2, focusing on the relative proportion with low BMD. Low BMD was present in 40% of current smokers compared with 20% of nonsmokers ($P = .17$). A substantially higher proportion of low BMD was observed in men (36%) than in women (16%) ($P = .06$), and a strong differential was noted between those with a height Z-score of ≤ -1 (48% with low BMD) compared with a height Z-score of > -1 (11% with low BMD) ($P < .001$). Current smokers tended to have a higher likelihood of a low BMD, as did subjects with an abnormally low peak GH level or an abnormally low IGF-I level; however, random variability could not be ruled out as an explanation for these latter differences. There was some indication, although not statistically precise, that cranial radiation therapy of ≥ 24 Gy may be a risk factor for low BMD. BMI category did not appear to be associated with prevalence of low BMD, nor did fasting insulin level.

Because prevalence of low BMD appeared to differ substantially by sex and by height, we evaluated the interactive effect of sex and height Z-score on low BMD. Although men were more likely than

TABLE 1
Demographics and Study Variables by Sex and Low Bone Mineral Density Status

	Total (n=74)		Men (n=31)		Women (n=43)		P	Normal BMD* (n=56)		Low BMD* (n=18)		P
	Mean	(SD)	Mean	(SD)	Mean	(SD)		Mean	(SD)	Mean	(SD)	
Age at interview, y	30.04	(7.23)	30.84	(7.39)	29.45	(7.14)	.42	29.48	(7.07)	31.75	(7.65)	.25
Age at diagnosis, y	5.64	(4.34)	6.05	(5.07)	5.34	(3.77)	.49	5.37	(4.39)	6.47	(4.21)	.35
Survival time, y	24.4	(4.84)	24.79	(4.86)	24.11	(4.87)	.56	24.11	(4.75)	25.28	(5.17)	.38
Height, cm	166.01	(9.06)	171.84	(7.68)	161.8	(7.57)	<.01	166.77	(8.77)	163.62	(9.77)	.20
Height Z-score†	-0.65	(1.22)	-1.06	(1.33)	-0.35	(1.04)	.01	-0.39	(1.13)	-1.44	(1.15)	<.01
Weight, kg	74.18	(17.27)	78.72	(17.60)	70.90	(16.45)	.05	74.72	(16.41)	72.47	(20.13)	.63
Body mass index, kg/m ²	26.87	(5.85)	26.50	(5.00)	27.14	(6.43)	.64	26.90	(5.80)	26.79	(6.18)	.95
Percent body fat	33.22	(11.07)	26.08	(8.15)	38.36	(10.04)	<.01	33.53	(10.96)	32.24	(11.67)	.67
Fat mass, kg	25.12	(12.17)	21.36	(10.3)	27.82	(12.8)	.02	25.42	(11.99)	24.19	(13.03)	.71
Lean mass, kg	45.36	(10.60)	53.74	(9.14)	39.32	(6.81)	<.01	45.4	(10.38)	45.23	(11.55)	.95
Bone mass, kg	2.71	(0.57)	3.03	(0.57)	2.47	(0.45)	<.01	2.79	(0.55)	2.43	(0.54)	.02
Thyroxine, ng/dL	1.07	(0.17)	1.05	(0.15)	1.07	(0.18)	.60	1.06	(0.18)	1.10	(0.13)	.38
TSH, mU/L	2.58	(3.96)	2.08	(0.97)	2.95	(5.15)	.29	2.71	(4.53)	2.18	(1.05)	.42
Insulin, mU/L	8.11	(7.92)	6.68	(4.35)	9.14	(9.64)	.14	8.21	(8.11)	7.78	(7.53)	.84
Peak growth hormone, µg/L	28.13	(35.13)	18.53	(29.93)	34.76	(37.21)	.06	31.07	(36.4)	18.79	(29.78)	.21
IGF-I Z-score (ARUP)	-0.75	(0.88)	-0.59	(0.88)	-0.88	(0.87)	.17	-0.66	(0.81)	-1.04	(1.05)	.12
IGF-I Z-score (Esoterix)	-1.23	(0.76)	-1.19	(0.77)	-1.27	(0.76)	.67	-1.14	(0.74)	-1.51	(0.77)	.08
Bone mineral density Z-scores												
Femoral neck	0.18	(1.07)	0.14	(1.26)	0.21	(0.93)	.77	0.55	(0.90)	-0.97	(0.70)	<.01
Lumbar (L2-L4)	0.13	(1.14)	0.13	(1.38)	0.14	(0.96)	.96	0.54	(0.97)	-1.12	(0.60)	<.01
Total body	0.34	(1.05)	0.46	(1.16)	0.25	(0.97)	.41	0.65	(0.95)	-0.63	(0.70)	<.01
Lowest Z-score (any site)	-0.25	(1.02)	-0.26	(1.21)	-0.24	(0.86)	.96	0.14	(0.83)	-1.44	(0.48)	<.01

BMD indicates bone mineral density; SD, standard deviation; TSH, thyroid stimulating hormone; IGF-I, insulin-like growth factor 1.

*Low bone mineral density was defined as a Z-score ≤ -1 ; normal bone mineral density was defined as a Z-score of > -1 .

†Calculated with age-specific and sex-specific National Health and Nutrition Examination Survey norms for non-Hispanic whites.

women to be shorter than expected based on population norms (≤ -1 SD for height), the odds of having prevalent low BMD among short women compared with nonshort women (OR, 12.50; 95% CI, 1.95-80.25) was considerably stronger than that of short men compared with nonshort men (OR, 4.00; 95% CI, 0.81-19.82). The male-female difference in BMD (lowest Z-score of any site evaluated) by height Z-score is illustrated in the 2 panels of Figure 1. For women, a fairly strong linear correlation ($r = 0.64$; $R^2 = 0.42$ [$P < .001$]) between BMD and height Z-score is observed, whereas in men the evidence for a linear correlation was substantially weaker ($r = 0.23$; $R^2 = 0.051$ [$P = .22$]).

DISCUSSION

In this long-term follow-up study of young adult survivors of childhood ALL, we found that 24% of subjects had an abnormally low BMD based on DXA scan results. Several studies have been published both supporting and refuting the premise that low BMD is a significant negative outcome for childhood

ALL survivors because of their disease, treatment, or associated effects.^{3,5,7,19,39,40} Arikoski et al found decreased BMD in both the lumbar and femoral regions among 29 survivors of ALL who had received cranial irradiation and were tested approximately 8 years after completion of therapy.³ Brennan et al found low BMD values among 31 adults who were examined approximately 17.8 years after ALL diagnosis.³⁹ In contrast, Kadan-Lottick et al, although they demonstrated decreased BMD during maintenance therapy in children treated for ALL, reported BMD recovery in the same children shortly after completion of therapy.⁶ Both Van der Sluis et al and Lequin et al also found that, even in children treated for ALL with high-dose dexamethasone and methotrexate but not cranial irradiation, there were no significant long-term effects on height, BMD, or lean body mass and fat percentage at 10 years after treatment.^{7,41} To our knowledge, the current study is 1 of the larger studies that included a long time period from diagnosis, and provides some support for the hypothesis that a potential serious effect of childhood ALL and its treatment is low BMD in early adulthood.

TABLE 2
Demographics and Clinical Characteristics in Participants With Low Bone Mineral Density

	Total No.	Low BMD*		P	OR†	95% CI
		No.	(%)			
Sex				.06		
Female	43	7	(16.3)		Referent	
Male	31	11	(35.5)		2.83	0.95-8.45
Age group at interview, y				.53		
19-29	39	8	(20.5)		Referent	
30-39	27	7	(25.9)		1.36	0.43-4.33
40-45	8	3	(37.5)		2.33	0.46-11.85
Year diagnosed				.60		
1970-1979	33	9	(27.3)		1.33	0.46-3.87
1980-1986	41	9	(22.0)		Referent	
Cranial radiation treatment				.24		
None	25	5	(20.0)		Referent	
<24 Gy	24	4	(16.7)		0.80	0.19-3.42
≥24 Gy	25	9	(36.0)		2.25	0.63-8.06
Cranial radiation treatment				.09		
0-23 Gy	49	9	(18.4)		Referent	
≥24 Gy	25	9	(36.0)		2.50	0.84-7.44
Current smoker				.17		
No	59	12	(20.3)		Referent	
Yes	15	6	(40.0)		2.61	0.78-8.77
Oral contraceptives (female)				.39		
No	27	3	(11.1)		Referent	
Yes	16	4	(25.0)		2.67	0.51-13.88
Height Z-score‡				<.01		
Z-score ≤ -1	27	13	(48.1)		7.80	2.36-25.79
Z-score > -1	47	5	(10.6)		Referent	
Height Z-score‡				.03		
Z-score ≤ -2.25	6	4	(66.7)		7.71	1.28-46.50
Z-score > -2.25	68	14	(20.6)		Referent	
Body mass index, kg/m ²				.74		
Normal (<25)	34	9	(26.5)		Referent	
Overweight (25-29.9)	18	3	(16.7)		0.56	0.13-2.38
Obese (>30)	22	6	(27.3)		1.04	0.31-3.49
Peak growth hormone, µg/L				.47		
Normal (>16.5)	26	4	(15.4)		Referent	
Insufficient (9-16.5)	13	4	(30.8)		2.44	0.50-11.97
Deficient (<9)	32	9	(28.1)		2.15	0.58-8.02
Peak growth hormone, µg/L				.20		
Normal (>16.5)	26	4	(15.4)		Referent	
Low (≤16.5)	45	13	(28.9)		2.23	0.64-7.76
IGF-I: ARUP Laboratories reference range				.17		
Normal	65	15	(23.1)		Referent	
Low	6	3	(50.0)		3.33	0.61-18.27
IGF-I: Esoterix reference range				.01		
Normal	47	7	(14.9)		Referent	
Low	24	11	(45.8)		4.84	1.55-15.05

BMD indicates bone mineral density; OR, odds ratio; 95% CI, 95% confidence interval; Gy, grays; IGF-I, insulin-like growth factor 1.

*Low bone mineral density was defined as a Z-score ≤ -1.

†Relative odds of having low BMD.

‡Calculated with age- and sex-specific National Health and Nutrition Examination Survey norms for non-Hispanic whites.

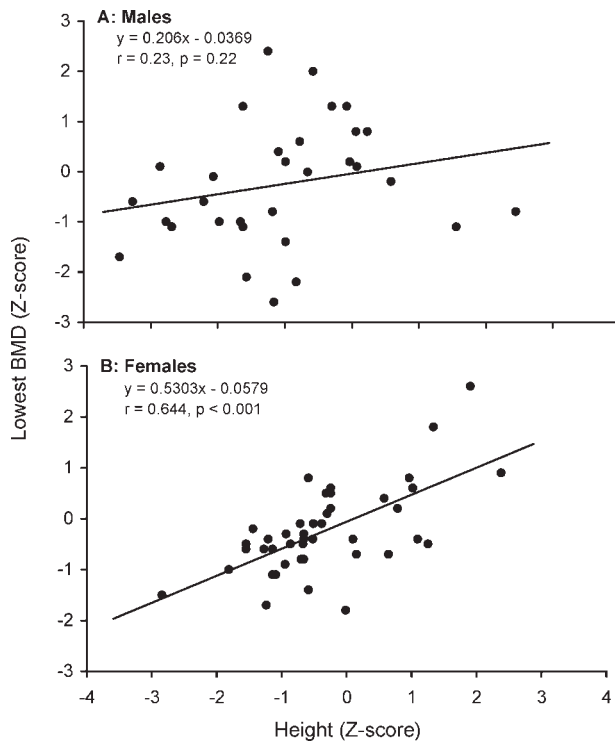


FIGURE 1. The correlation between bone mineral density (BMD) and height by sex in (A) men and (B) women is shown.

According to the World Health Organization, 11.2% of 30-year-old men and 18.8% of 30-year-old women have low BMD.⁴² Although manufacturer norms differ across DXA machines, thus making direct comparisons tenuous, we found an opposite sex effect: low BMD was present in a higher percentage of men compared with women (36% of men and 16% of women). Low BMD more often afflicts women than men,^{37,43} although the sex difference we observed in ALL survivors has been noted previously.^{3,20,44,45} Male subjects in our sample were not as heavy on average (based on BMI) as the female subjects, but BMI did not appear to be a risk factor for low BMD in this study. A heavier weight has arguably been considered to be a protective measure against low BMD⁴⁶; however, heavy weight may interfere with the accuracy of a DXA scan, so this phenomenon must be viewed cautiously.⁴⁷

Approximately one-third of our female survivors were using oral contraceptives (OCPs) for birth control. Although it had been debated that the estrogen in the OCPs is protective for bone density,^{48,49} the recent decrease in doses and variety of estrogen products may no longer be a guarantee that they are protective.^{50,51} One of our male subjects (without low BMD) was receiving testosterone replacement ther-

apy. Although estrogen is considered the more important hormone in regulating bone mass in men, testosterone may have some independent effects on bone formation and resorption and provide the substrate needed for aromatization to estrogen.⁵² Androgen replacement is more difficult in men and usually is preceded by an extensive endocrine investigation before commencement of therapy. It is possible that some of the men who had low BMD may have had an unrecognized testosterone deficiency.

Although these data provided some support for our hypothesis that chronic GH insufficiency would be associated with low BMD (28.9% of those with a peak GH of ≤ 16.5 $\mu\text{g/dL}$, vs 15.4% of subjects with peak GH > 16.5 , had low BMD), we could not reliably rule out the possibility that this difference occurred because of random variability ($P = .20$). Because some of these survivors likely developed GH deficiency during childhood, it is possible they were unable to achieve optimal bone mass, leaving them with an inadequate skeletal mineral foundation for adult life.⁵³

Our finding that low BMD was associated with lower mean IGF-I Z-score is similar to that reported by Reed et al, who demonstrated lower IGF-I levels in a group of adults (aged 44 ± 12 years) who had idiopathic osteoporosis.⁵⁴ Although IGF-I can be influenced by many factors, including poor nutrition and acute and chronic illness,⁵⁵ lower IGF-I levels could represent a problem with bone mineralization among ALL survivors, because it directly affects the function of osteoblasts.²²

The results of the current study should be interpreted with consideration for potential study limitations. BMD measurements from DXA are dependent on area (length and size), but do not take into account bone depth (volumetric density).^{56,57} In individuals who are very short, measurements may not be reliable.^{56,57} Some have advocated calculating volumetric BMD in these situations,^{58,59} but because 89% of the adult survivors in the current study had a height within 2 SD of the NHANES age-specific, race-specific, and sex-specific normative means,³⁸ we chose not to adjust their BMDs using bone mineral apparent density calculations. An alternative suggestion could be to use quantitative computed tomography to further assess volume and bone geometry, but this requires a significant increase in exposure to ionizing radiation and is not broadly available.⁵⁷ Furthermore, although the results may be in the osteopenic or osteoporotic range, this does not necessarily equate to bone strength.⁵⁷ It is recommended by the International Society for Clinical Densitometry that the diagnosis of low BMD in

younger individuals should not be decided solely on densitometric criteria, because the this categorization was designed initially to classify postmenopausal white women and their risk for fracture.³⁷ Z-scores were identified to help decipher the values for younger individuals, but the fracture risk and clinical significance has not yet been well determined.³⁷

Interpreting IGF-I values in our study was difficult because of the wide variability in the normative values set by individual laboratories. Our assay was completed through ARUP Laboratories, whose reference values were much lower than another widely used reference laboratory, Esoterix. On the basis of the recommendation from Granada et al, we decided to present our IGF-I values as standard deviations, which allowed a more uniform interpretation of the age-related and sex-related data.^{34,60} It may be helpful for clinicians who care for cancer survivors to test for IGF-I levels along with their normal screening laboratories. If IGF-I is on the lower side of normal or frankly abnormal, it may be advisable to obtain a baseline DXA scan to document BMD and initiate treatment with calcium and vitamin D or other therapies as necessary.

The data from the current study were consistent with previous evidence suggesting that smoking may increase risk for low BMD.^{61,62} In addition, our results arguably provide some indication that cranial radiation exposure of ≥ 24 Gy, but not lower doses, was associated with decreased BMD (OR of 2.50 for a BMD Z-score of ≤ -1 among those who received ≥ 24 Gy vs < 24 Gy or none [95% CI, 0.84-7.44]). Although this finding may be important to the bone health of current adult survivors of ALL who were treated with high doses of cranial radiation, modern ALL treatment for standard-risk and low-risk ALL no longer includes cranial irradiation⁶³ and therefore this potential risk factor is of limited relevance for most children treated today for ALL.

In conclusion, we found that 24% of the participants in the current study had a BMD of ≥ 1 SD below the mean, which is a higher percentage than expected based on the World Health Organization's report.⁴² This could not fully be explained by their GH status or IGF-I Z-score. Shorter women appeared to have a higher risk of developing low BMD than shorter men, although men overall had a substantially higher prevalence of low BMD than women. Further studies will need to be conducted to define the etiology of low BMD and predict risk factors for any related medical consequence for these ALL survivors as they age.

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