Dietary Protein Intake and Lean Muscle Mass in Survivors of Childhood Acute Lymphoblastic Leukemia: Report From the St. Jude Lifetime Cohort Study

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Background. Survivors of childhood acute lymphoblastic leukemia (ALL) are at risk for low lean muscle mass and muscle weakness, which may contribute to inactivity and early development of chronic diseases typically seen in older adults. Although increasing protein intake, in combination with resistance training, improves lean muscle mass in other populations, it is not known whether muscular tissue among survivors of ALL, whose impairments are treatment-related, will respond similarly.

Objective. The aim of this study was to evaluate associations among dietary protein intake, resistance training, and lean muscle mass in survivors of ALL and age-, sex-, and race-matched controls.

Design. This was a cross-sectional study.

Methods. Lean muscle mass was determined with dual-energy x-ray absorptiometry, dietary information with 24-hour recalls, and participation in resistance training with a questionnaire. Participants were 365 survivors of ALL (52% male; 87% white; median age=28.5 years, range=23.6–31.7) and 365 controls with no previous cancer.

Results. Compared with controls, survivors of ALL had lower lean muscle mass (55.0 versus 57.2 kg, respectively) and lower percentage of lean muscle mass (68.6% versus 71.4%, respectively) than controls. Similar proportions of survivors (71.1%) and controls (69.7%) met recommended dietary protein intake (0.8 g/kg/d). Survivors (45.4%) were less likely to report resistance training than controls (53.8%). In adjusted models, 1-g higher protein intake per kilogram of body mass per day was associated with a 7.9% increase and resistance training ≥1×wk, with a 2.8% increase in lean muscle mass.

Limitations. The cross-sectional study design limits temporal evaluation of the association between protein intake and lean muscle mass.

Conclusions. The findings suggest that survivors of childhood ALL with low lean muscle mass may benefit from optimizing dietary protein intake in combination with resistance training. Research is needed to determine whether resistance training with protein supplementation improves lean muscle mass in survivors of childhood ALL.

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Therapies for acute lymphoblastic leukemia (ALL) have acute and late effects on body composition. Loss of lean muscle mass[1] and gains in relative overall body mass[2] are reported during treatment and appear to persist long-term.[3] Loss of lean muscle mass is important because it is associated with reduced muscle strength,[4] bone density,[5] physical performance limitations,[4] markers of metabolic syndrome,[6] and early mortality.[7] Muscle weakness is common among survivors of childhood ALL,[3] who are twice as likely than siblings to report physical performance limitations,[8] 1.4 times more likely than members of the general population to have metabolic syndrome,[9] and 2.5 times more likely than siblings to experience early mortality.[8]

Research indicates that exposure to cranial radiation therapy (CRT) and damage to the growth hormone-producing ability of the pituitary gland[10] are significant risk factors for low lean muscle mass.[11,12] Among exposed survivors of ALL, this risk factor is unalterable without long-term growth hormone replacement therapy,[13] a treatment that is not completely without side effects.[14] Furthermore, sustainable and clinically significant long-term improvements in body composition and metabolic parameters following replacement with growth hormone have not been fully demonstrated in this population.[15,16] Recent evidence indicates that CRT is not the only risk factor associated with suboptimal body composition,[17,18] and that adopting a healthy lifestyle can positively influence body habits in this population.[17–19]

Although increasing protein intake, in combination with resistance training, improves lean muscle mass in other populations,[20–23] it is not known whether muscular tissue among survivors of ALL, whose impairments are treatment-related, will respond similarly. The objective of this study was to evaluate the specific contributions of dietary protein intake and resistance training to lean muscle mass among survivors of childhood ALL and an age-, sex-, and race-matched comparison group.

Method

Participants

Participants were enrolled from the St. Jude Lifetime Cohort Study (SJLIFE), a study designed to evaluate health outcomes among survivors of childhood cancer as they age. Cohort details and procedures have been described previously.[24,25] Individuals who were eligible for this cross-sectional analysis were diagnosed with ALL, treated at St. Jude Children's Research Hospital (SJCRH) between 1980 and 1999, at least 10 years from original diagnosis, and 18 years of age or older. People with congenital cognitive, musculoskeletal, or cardiopulmonary impairments; who were pregnant or lactating; or who were currently being treated for cancer were not eligible. Potentially eligible participants were stratified by sex, time since diagnosis ($<$25 years, $\geq$25 years), and whether they were exposed to cranial radiation during treatment. Survivors were randomized within stratum and simultaneously recruited across strata. To obtain a representative sample of the SJCRH ALL survivor population treated between 1980 and 1999, accrual was carefully monitored to ensure that the final sample matched the distribution of eligible survivors in each of the 4 strata within the radiation category.

To recruit a comparison group (controls), frequency matched to survivors of ALL by race, age, and sex, a random sample of family members of SJCRH patients (not including SJLIFE participants) was selected. Parents of patients were contacted prior to an upcoming clinic appointment to determine whether they, or other adult family members and friends, were interested in participating. A roster of interested family members and friends was created from which study staff selected individuals fulfilling matching criteria, screened them for eligibility, and invited them to participate. Inclusion and exclusion criteria for controls were the same as those for survivors, except that controls did not have a history of childhood cancer. Although adult onset cancer was not one of the exclusion criteria, none of the controls reported a cancer history. Participants provided written informed consent

prior to any testing or questionnaire completion.

Measurements

Anthropometrics and lean muscle mass. Anthropometric measurements were taken, including height (in centimeters) as measured with a wall-mounted stadiometer (SECA, Dundalk, Maryland), weight (in kilograms) as measured with an electronic scale (Scale-Tronix, White Plains, New York), and waist circumference (in centimeters) at the narrowest point between the anterior superior iliac crest and the lowest rib (Gulick tape measure, Patterson Medical, Warrenville, Illinois). Body mass index was calculated by dividing weight (in kilograms) by height (in meters squared), and waist-to-height ratio was calculated by dividing waist circumference by height.

Whole-body dual-energy x-ray absorptiometry (DXA) was performed to estimate body composition (Hologic Model QDR 4500 Fan-Array Scanner and APEX 2.3.1 software, Hologic Inc, Bedford, Massachusetts).[26–30] The scanner was calibrated weekly with known phantoms to minimize machine drift. Body regions were isolated using regional computer-generated default lines with manual adjustment, as described by Kim et al.[31] Total fat mass and total fat-free mass measurements were recorded. Percentage of body fat and percentage of lean body mass were calculated by dividing fat mass and fat-free mass by total body mass and multiplying the result by 100.[32–35] Relative lean muscle mass was calculated by dividing lean muscle mass (in kilograms) by height (in meters) and converting the result to an age-, sex-, and race-specific z score using published data from the National Health and Nutrition Examination Survey (NHANES).[36]

Dietary intake. To estimate usual food and nutrient intake, trained interviewers conducted three 24-hour dietary recalls.[37,38] The first recall was an in-person interview done at the time of anthropometric assessment. Subsequent interviews were conducted via telephone so that the recalls represented 2 nonconsecutive weekdays and 1 weekend day over a 1-month period. A standardized multiple-pass approach was used to capture types and amounts of foods and beverages consumed during a 24-hour period (midnight–midnight) for the day preceding the interview.[39] The Nutrition Data System for Research (NDS-R) dietary data collection software (version 2008–2012, University of Minnesota, Minneapolis, Minnesota) includes a database of more than 18,000 foods, including ethnic foods and more than 7,000 brand-name foods, with values for 163 nutrients, nutrient ratios, and other food components. Final calculations for analysis were completed using the NDS-R 2012. Data are reported as daily averages of kilocalories, sodium, fiber intake, and kilocalories of fat, protein, and carbohydrates. Calories from protein were converted into grams of protein and divided by total body mass in order to compare participants' protein intake with the Dietary Reference Intake recommended value of 0.8 g of protein per kilogram of body weight.[40]

ALL treatment. Trained abstractors examined participants' medical records for detailed information on cancer treatment. Variables included to describe the study population were cumulative doses of anthracyclines (in doxorubicin equivalents)[41]; antimetabolites, vincristine, epipodophyllotoxins, asparaginase, and glucocorticoids (in prednisone equivalents)[42]; and CRT. Cranial radiation was categorized as none, 1 to 19 Gy, or ≥20 Gy in analysis.

Lifestyle factors. Demographic and lifestyle information, obtained by having participants complete detailed questionnaires, included age at examination, sex, race (white, black, other), smoking status (never, past, current), annual household income (≤$19,999, $20,000–$79,999, and ≥$80,000), education (less than high school, high school graduate, college), and employment status (employed, student, retired, unemployed, disabled).

Participation in regular resistance training was ascertained by a single question from the Rapid Assessment of Physical Activity;[14] individuals who responded "yes" to a question that asked whether they participated in activities to increase muscle strength once a week or more frequently were categorized as participants. Physical activity patterns were calculated from accelerometer-obtained movement data. Participants wore the device (ActiGraph, model GT3X, and ActiLife version 6.1, ActiGraph LLC, Pensacola, Florida) on the right hip during nonbathing, nonswimming waking hours for 7 consecutive days, and 1-minute epochs were used to correspond to data collected in the NHANES study. Manufacturer-provided software were used to process data. Conversions based on the *2011 Compendium of Physical Activities* were used to calculate metabolic equivalent minutes per week (MET minutes per week) (sedentary=1, light activity=2.25, moderate activity=4.5, and vigorous activity=9).[43]

Data Analysis

Descriptive statistics were used to summarize characteristics of the study population and were compared between survivor participants and eligible nonparticipant survivors and controls, using Wilcoxon sign rank tests or chi-square statistics as appropriate. Means and standard deviations were calculated for body composition and dietary variables and compared between survivors and controls with 2-sample t tests.[44] Multivariable analyses were used to evaluate the contributions of daily intake of dietary protein (in grams per kilogram of body mass) and participation in regular resistance training (independent variables) to lean muscle mass (in kilograms) and waist-to-height ratio (dependent variables: 2 separate models) among survivors. In addition to protein intake and participation in regular resistance training, models included the following covariates: CRT,[45] age, sex, race, and physical activity level. To evaluate the potential differential contribution of daily dietary protein intake between survivors and controls, an additional multivariable model was constructed that included both main effects and an interaction term for survivor status and protein intake. Variables were entered simultaneously into all models. These analyses were a secondary aim of our overall study. The sample size for the larger study was determined a priori and designed to detect a 10% difference

Table 1.
Characteristics of Acute Lymphoblastic Leukemia Survivor Participants and Nonparticipants[a]

Variable	Participants (n=365)	Nonparticipants (n=51)	*P*
Age (y), median (range)	28.5 (18.4–44.6)	27.3 (18.0–45.9)	.09
Diagnosis age (y), Median (range)	5.1 (0.6–18.8)	4.6 (2.1–18.8)	.65
Survival time (y), median (range)	21.9 (11.0–30.7)	20.3 (11.3–27.8)	.11
Sex, n (%)			
Male	174 (47.7)	25 (49.0)	.89
Female	191 (52.3)	26 (51.0)	
Race, n (%)			
Black	44 (12.1)	5 (9.8)	.89
White	317 (86.8)	46 (90.2)	
Other	4 (1.1)	0 (0.0)	
Cranial radiation	149 (40.8)	18 (35.3)	.13
Glucocorticoids			
Prednisone, n (%)	365 (100.0)	51 (100.0)	
Median (range), mg/m^2	2,240 (200–23,600)	9,650 (1,120–11,800)	<.001
Dexamethasone, n (%)	75 (20.5)	6 (11.7)	
Median (range), mg/m^2	1,568 (72–12,880)	1,568 (1,400–1,624)	.83
Hydrocortisone (IT), n (%)	291 (79.7)	47 (92.2)	
Median (range)	391 (18–105)	369 (104–762)	.38
Antimetabolites			
Methotrexate (IV), n (%)	320 (87.7)	46 (90.2)	
Median (range), mg/m^2	14,757 (449–40,571)	13,424 (4,753–25,683)	.89
Methotrexate (IT), n (%)	365 (100.0)	51 (100.0)	
Median (range), mg	156 (12–458)	162 (80–336)	.62
6-mercaptopurine, n (%)	357 (97.8)	51 (100.0)	
Median (range), mg/m^2	47,250 (5,994–130,900)	47,250 (6,185–74,900)	.48
Cytarabine (IT), n (%)	298 (81.6)	48 (94.1)	
Median (range), mg/m^2	576 (73–11,516)	565 (108–1,142)	.38
Vincristine, n (%)	365 (100.0)	51 (100.0)	
Median (range), mg/m^2	47 (3–105)	54 (5–118)	.06
Anthracyclines			
Daunorubicin, n (%)	242 (66.3)	40 (78.4)	
Median (range), mg/m^2	75 (24–451)	87 (48–158)	.84
Doxorubicin, n (%)	40 (11.0)	3 (5.9)	
Median (range), mg/m^2	179 (25–324)	169 (151–187)	1.00
Epipodophyllotoxins			
Etoposide, n (%)	223 (61.1)	36 (70.6)	
Median (range), mg/m^2	9,462 (400–23,630)	9,978 (883–16,215)	.54
Teniposide, n (%)	220 (60.3)	28 (54.9)	
Median (range), mg/m^2	3,241 (150–10,339)	3,478 (597–7,983)	.84
Asparaginase			
E coli asparaginase, n (%)	361 (98.9)	51 (100.0)	
Median (range), IU/m^2	701,979 (4,000–99,246)	92,051 (40,308–347,783)	.01
Erwinase,[b] n (%)	46 (12.9)	5 (9.8)	
Median (range), IU/m^2	54,980 (10,000–118,507)	113,398 (20,000–247,083)	.42

[a] IV=intravenous, IT=intrathecal, IU=international unit.
[b] Porton Biopharma Ltd, Salisbury, Wiltshire, United Kingdom.

between cases and the comparison group on measures of physical fitness and performance.[46] Analysis was performed using SAS 9.3 software (SAS Institute Inc, Cary, North Carolina).

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Results

Among 416 potentially eligible survivors of ALL, 51 (12.5%) declined participation, and 365 (87.5%) completed a study visit. Among 451 potentially eligible controls, 86 (19.1%) declined participation, and 365 (80.9%) completed a study visit. Characteristics of survivor participants and eligible nonparticipants are shown in Table 1. Participants did not differ from nonparticipants by age, sex, race or ethnicity, age at diagnosis, time since diagnosis, or current age. Types and doses of chemotherapy were similar between survivor participants and nonparticipants, except for prednisone equivalent dose. Study participants were 47.7% male, had a median age of 28.5 years (range=18.4–44.6) at evaluation, and had a median survival time since diagnosis of 21.9 years (range=11.0–30.7). Because they were matched by sex, race, and 5-year age groups, the control group had the same demographic distribution as ALL survivor participants.

Lifestyle factors are shown in Table 2. There were no differences between survivors of ALL and comparison group members for physical activity levels, smoking status, educational attainment, or employment status. Survivors were less likely than controls to report participation in regular resistance training (45.4% versus 53.8%, χ^2 [1 *df*]=4.97, $P<.03$), and to have an annual household income of ≥$80,000 per year (21.5% versus 29.7%, χ^2 [1 *df*]=5.56, $P=.02$).

Table 2.
Lifestyle Variables Among Survivors of Acute Lymphoblastic Leukemia and Comparison Group

Lifestyle Factors[a]	Survivors (n=365)	Comparison Group (n=365)	*P*
Smoking status			
Never	236 (64.7)	220 (61.8)	.67
Past	38 (10.4)	37 (10.4)	
Current	91 (24.9)	99 (27.8)	
Education			
<High school	40 (11.5)	33 (9.5)	.19
High school graduate	81 (23.3)	65 (18.8)	
College	227 (65.2)	248 (71.7)	
Employment status			
Employed,[b] student, or retired	263 (75.4)	277 (82.2)	.08
Unemployed	75 (21.5)	54 (16.0)	
Disabled	11 (3.1)	6 (1.8)	
Household income			
≤$19,999	62 (20.9)	65 (21.5)	.02
$20,000–$79,999	171 (57.6)	148 (48.8)	
≥80,000	64 (21.5)	90 (29.7)	
Resistance training ≥once/wk			
Yes	162 (45.4)	183 (53.8)	.03
No	195 (54.6)	157 (46.2)	
MET min/wk	1,564.1 (1,517.4 to 1,610.7)	1,613.7 (1,564.1 to 1,663.2)	.15

[a] Lifestyle factors are reported as number (%), except for metabolic equivalent (MET) minutes/week, which is reported as mean (95% confidence interval).
[b] Employed includes individuals who identified themselves as a homemaker or caregiver.

Body Composition

Measurements of body composition are shown in Table 3. Survivors of ALL and controls had similar mean body weights. However, survivors were shorter than controls and thus had a higher body mass index and a higher waist-to-height ratio. These increases were accounted for by higher fat mass. Absolute lean muscle mass and percentage of lean muscle mass were lower among survivors of ALL than among controls. However, lean muscle mass relative to height did not differ between survivors and controls. Seven percent of survivors of ALL and 5% of the control group had relative lean muscle mass z scores of −1.3 or greater using published population values.[36]

Dietary Intake

Dietary intake data are shown in Table 3. There were no differences between survivors of ALL and the control group for any dietary parameters. Notably, calories from protein and calories from protein standardized by total body mass did not differ between groups. Furthermore, the proportion of individuals who met the daily Dietary Reference Intake[40] recommended amount of protein did not differ between survivors of ALL and controls.

Protein Intake and Lean Muscle Mass in Survivors of ALL

Table 4 shows the results of multivariable models evaluating associations between daily dietary protein intake (in grams) and waist-to-height ratio and percentage of lean body mass among survivors. Both protein intake and strength training were significantly associated with either waist-to-height ratio or percentage of lean muscle mass. Protein intake, age, sex, MET minutes per week, CRT, and resistance training explained 31% of the variability in waist-to-height ratio and 56% of the variability in per-

Table 3.
Body Composition and Dietary Intake Among Survivors of Acute Lymphoblastic Leukemia and Comparison Group[a]

Variable	Survivors (n=365)	Comparison Group (n=365)	P[b]
Body composition			
Height (cm)	168.5 (167.4, 169.5)	171.9 (170.9, 172.9)	<.001
Weight (kg)	81.4 (79.1, 83.7)	81.4 (79.1, 83.6)	.99
Lean muscle mass (kg)	55.0 (53.6, 56.4)	57.2 (55.9, 58.6)	.03
Percentage of lean muscle mass	68.6 (67.7, 69.5)	71.4 (70.4, 72.5)	<.001
Relative lean muscle mass	19.2 (18.8, 19.6)	19.2 (18.9, 19.5)	.98
Waist circumference (cm)	89.7 (88.0, 91.4)	86.0 (84.4, 87.6)	.001
Body mass index (kg/m^2)	28.6 (27.9, 29.4)	27.5 (26.8, 28.2)	.03
Waist-to-height ratio	0.53 (0.52, 0.54)	0.50 (0.49, 0.51)	<.001
Fat mass (kg)	26.3 (25.0, 27.7)	24.1 (22.8, 25.5)	.02
Percentage of fat mass	31.4 (30.5, 32.3)	28.6 (27.5, 29.6)	<.001
Appendicular lean muscle mass (kg)	24.2 (23.5, 24.9)	25.4 (24.7, 26.1)	.02
Dietary intake			
Average kcal/d	1,995.3 (1,535.6–2,543.4)	2,054.7 (1,602.2–2,476.6)	.18
Kilocalories per day/total mass	25.6 (19.3–33.0)	25.9 (19.3–32.5)	.59
Fat (kcal)	686.0 (510.7–910.1)	692.2 (518.0–896.0)	.68
Fat/total mass (kcal/kg)	8.8 (6.5–11.7)	8.7 (6.2–11.6)	.94
Protein (kcal)	313.9 (240.7–408.4)	312.5 (246.8–422.1)	.85
Protein/total mass (kcal/kg)	4.0 (3.0–5.4)	4.1 (2.9–5.4)	.79
Protein/total mass (g/kg)	1.0 (0.8–1.3)	1.0 (0.7–1.4)	.93
Carbohydrates (kcal)	965.2 (720.1–1,252.1)	938.1 (753.7–1,201.8)	.62
Carbohydrates/total mass (kcal/kg)	12.1 (8.9–16.9)	12.3 (8.8–16.3)	.91
Sodium (mg)	3,428.2 (2,656.2–4,237.9)	2,406.5 (2,679.0–4,300.4)	.73
Total fiber (g)	12.5 (9.4–16.8)	13.6 (10.3–18.5)	.14
Dietary reference level, n (%)			
≥0.8 g protein per kilogram of body weight	251 (71.1%)	235 (69.7%)	.69
<0.8 g protein per kilogram of body weight	102 (28.9%)	102 (30.3%)	

[a] Body composition variables are reported as mean (95% confidence interval). Dietary variables are reported as median (interquartile range [first and third quartiles]) because the data were not normally distributed.
[b] *P* values are from median 2-sample *t* tests.

centage of lean muscle mass. There was no interaction between CRT status and protein intake, indicating that effects of protein intake on lean muscle mass did not differ among survivors who were and those who were not exposed to CRT.

Protein Intake and Lean Muscle Mass Among Survivors of ALL and Controls

Table 5 shows the association between relative protein intake and percentage of lean muscle mass. This linear model explained 58% of the variability in percentage of lean muscle mass with age, sex, physical activity, resistance training, relative protein intake, and survivor status included in the model. For each gram of protein per kilogram of body mass, lean muscle mass increased by 7.9%; participation in resistance training increased lean muscle mass by 2.8%. There was no interaction (data not shown) between survivor status and relative protein intake, indicating that the effects of protein intake on lean muscle mass did not differ between survivors and controls.

Discussion

In this large, well-characterized population of adult survivors of childhood ALL, we found an independent association between dietary protein intake and lean muscle mass. This association persisted after accounting for CRT exposure, sex, age, race, smoking, physical activity, and participation in regular resistance training. Additionally, the association between protein intake and lean muscle mass did not differ between ALL survivors and an age-, sex-, and race-matched comparison group, even

Table 4.
Association Between Dietary Protein Intake and Body Composition Among Survivors of Acute Lymphoblastic Leukemia[a]

Variable	Waist-to-Height Ratio[b]					Proportion of Lean Body Mass[c]				
	β	SE	LCL	UCL	*P*	*β*	SE	LCL	UCL	*P*
Protein	–.0772	.0100	–.0968	–.0576	<.001	.0777	.0079	.0622	.0932	<.001
Age	.0029	.0008	.0013	.0045	<.001	–.0009	.0006	–.0021	.0003	.13
Sex										
Female	–.0080	.0089	–.0254	.0094	.37	–.0938	.0070	–.1075	–.0801	<.001
Male	Ref					Ref				
MET min/wk	–.0001	.0001	–.0003	.0001	.37	.0001	.0001	–.0001	.0003	.12
CRT										
<24 Gy	.0443	.0103	.0241	.0645	<.001	–.0344	.0081	–.0503	–.0185	<.001
≥24 Gy	.0408	.0146	.0122	.0694	.005	–.0432	.0113	–.0653	–.0211	<.001
None	Ref					Ref				
Resistance training										
Yes	–.0188	.0089	–.0362	–.0014	.04	.0127	.0069	–.0008	.0262	.07
No	Ref					Ref				

[a] Multiple linear regression models were used to generate beta coefficients, standard errors, confidence intervals, and *P* values. *β*=beta coefficient, SE=standard error, LCL=lower 95% confidence limit, UCL=upper 95% confidence limit, Ref=reference group, MET=metabolic equivalent, CRT=cranial radiation therapy.
[b] *R*-squared value for the waist-to-height ratio model was .31.
[c] *R*-squared value for the percentage of lean body mass model was .56. Age at assessment was removed from the percentage of lean muscle mass model because it was found to be nonsignificant.

though survivors had lower mean values for actual lean muscle mass and percentage of lean muscle mass. These findings are good news for survivors of childhood ALL with reduced lean muscle mass, suggesting that optimizing dietary protein intake may help remediate this problem. Our data also indicate that resistance training and exercise are associated with higher lean muscle mass.

Table 5.
Association Between Protein Intake and Body Composition for Survivors of Acute Lymphoblastic Leukemia and Control Group[a]

Variable	Proportion of Lean Body Mass				
	β	SE	LCL	UCL	*P*
Protein	.0789	.0057	.0677	.0901	<.001
Age	–.0021	.0004	–.0029	–.0013	<.001
Sex					
Female	–.0909	.0051	–.1009	–.0809	<.001
Male	Ref				
MET min/wk	.0001	.00004	.0000	.0002	.001
Participant					
Survivor group	–.0243	.0049	–.0339	–.0147	<.001
Control group	Ref				
Resistance training					
Yes	.0283	.0051	.0183	.0383	<.001
No	Ref				

[a] A multiple linear regression model was used to generate beta coefficients, standard errors, and *P* values. An interaction term between participant status and protein intake was removed from the final model because it was found to be nonsignificant. *R*-squared value for the model was=.58. *β*=beta coefficient, SE=standard error, LCL=lower 95% confidence limit, UCL=upper 95% confidence limit, Ref=reference group.

Our findings regarding body composition are consistent with previous reports in the ALL survivor population.[1–3,47] Tonorezos et al,[47] in a study of 117 adult survivors of childhood ALL, reported that those exposed had a mean lean muscle mass of 47.8 kg (SD=12.4) compared with survivors not exposed to CRT who had a mean lean muscle mass of 52.7 kg (SD=11.0). Our slightly older survivor population, with a higher proportion of male participants, had a modestly higher mean lean muscle mass of 55.0 kg, which was still lower than the mean lean muscle mass (57.2 kg) in our age-, sex- and race-matched comparison group. Our finding that survivors of ALL had, on average, larger waist circumferences than comparison group members is of clinical significance, as risk for mortality increases by 9% for every 5-cm increase in waist circumference.[48]

We were unable to identify other published studies that examined the association between dietary protein intake and lean muscle mass in the childhood ALL survivor population. However, observa-

tional studies among older adults and intervention studies among women who were overweight or obese and among people with cystic fibrosis and rheumatoid arthritis showed similar associations.[48–52] In a report from the Health, Aging, and Body Composition Study, a study of older adults at risk for low lean muscle mass, Houston et al[48] reported that daily protein intake of 1.2 g per kilogram of body mass was associated with a 43% less loss of lean muscle mass compared with a daily protein intake of 0.8 g per kilogram of body mass. Another study among older adults showed that dietary protein intake explained 76.4% of the variation in lean muscle mass and that a 1-unit increment in protein intake was associated with 2.7% higher lean muscle mass.[49] In a weight loss study (750 kcal/d deficient) among women who were overweight or obese, the group randomized to receive 1.4 g per kilogram of protein per day lost 1.3 kg less lean muscle mass than the group receiving 0.82 g per kilogram of protein per day.[50] In a study of protein supplementation (20%–40% increase over 6 months) among children with cystic fibrosis who were more than 1 standard deviation below normal weight at baseline, Shepherd et al[51] reported a mean increase of 1.5 kg of lean muscle mass. Lastly, in a 12-week study among adults with rheumatoid arthritis with cachexia, Marcora et al[52] reported mean lean muscle mass increases of 0.61 to 0.84 kg with 2 different 7.2 g/d protein supplementation formulations.

We also found associations between resistance training and lean muscle mass among survivors of childhood ALL. This association is novel among survivors of ALL, but has been observed in studies among adults with other types of cancer or other chronic illnesses.[53–57] Lonbro et al,[57] in a study of head and neck cancer patients, demonstrated that 12 weeks of structured resistance training improved lean muscle mass by approximately 4% compared with self-selected physical activity. Similar studies have shown 4.0% to 6.5% increases in lean muscle mass after resistance training among people with chronic obstructive pulmonary disease,[55] type 2 diabetes,[56] and McArdle disease.[54]

There are limitations that should be taken into account when interpreting the results of this study. First, our participants were from a single institution and included those treated between 1980 and 1999. Even though the study population was carefully recruited to represent ALL survivors treated during this period, our results might not be generalizable to survivors of ALL treated at other institutions or those treated prior to 1980 or after 1999. Current treatment for ALL rarely includes CRT. Because CRT was associated with both of our outcomes, children treated without CRT are likely to be at less risk for higher waist-to-hip ratio and lower percentage of lean body mass. Second, our dietary assessment was based on self-report. Even though multiple 24-hour recall methods yield more reliable data than a food frequency questionnaire,[38] all recall data are subject to bias, and variation in diet within individuals is difficult to quantify. Because our study participants underreported their intake by about 30% in relation to their known energy requirements,[46] the reported mean intake of 1 g per kilogram of body weight was more likely 1.5 g per kilogram of body weight. Additionally, we did not have 100% participation in this study. It is possible that the health status of those individuals who opted to participate may have differed from those who chose not to participate, which has potential to bias our estimates. Finally, because this was a cross-sectional analysis, we do not know whether increasing protein intake and adding resistance exercise will improve lean muscle mass among survivors of ALL whose lean muscle mass is suboptimal. Because lean muscle mass is inherently tied to musculoskeletal fitness, which is key to overall well-being, injury prevention, functional independence, metabolic capacity, and maintenance of ideal body weight,[58] research is needed to address this question.

In conclusion, our study demonstrates a clear association among protein intake, resistance training, regular physical activity, and lean muscle mass in adult survivors of childhood ALL. As a result, we recommend that survivors of ALL without chronic kidney disease or conditions where a high protein diet is contraindicated[59] be counseled to eat a diet that includes at least 0.8 g of protein per kilogram of body mass per day. They also should be encouraged to participate in resistance training to support lean muscle mass. Thus, when treating survivors of childhood ALL, physical therapy professionals should include assessment of lean muscle mass as part of their comprehensive evaluation, prescribe resistance training for patients with low lean muscle mass, and refer individuals with inadequate protein in their diet for nutritional counseling.

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