

Obesity in Adult Survivors of Childhood Acute Lymphoblastic Leukemia: A Report from the Childhood Cancer Survivor Study

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Purpose: To determine whether adult survivors (≥ 18 years of age) of childhood acute lymphoblastic leukemia (ALL) are at increased risk for obesity and to assess patient and treatment variables that influence risk.

Patients and Methods: A retrospective cohort of participants of the Childhood Cancer Survivor Study was used to compare 1,765 adult survivors of childhood ALL to 2,565 adult siblings of childhood cancer survivors. Body-mass index (BMI; kilograms per square meter), calculated from self-reported heights and weights, was used to determine the prevalence of being overweight (BMI, 25-29.9) or obese (BMI ≥ 30.0). Polytomous logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for being overweight or obese among ALL survivors relative to the sibling control group.

Results: The age- and race-adjusted OR for being obese in survivors treated with cranial radiation doses ≥ 20 Gy

in comparison with siblings was 2.59 for females (95% CI, 1.88 to 3.55; $P < .001$) and 1.86 for males (95% CI, 1.33 to 2.57; $P < .001$). The OR for obesity was greatest among females diagnosed at 0 to 4 years of age and treated with radiation doses ≥ 20 Gy (OR, 3.81; 95% CI, 2.34 to 5.99; $P < .001$). Obesity was not associated with treatment consisting of chemotherapy only or with cranial radiation doses of 10 to 19 Gy.

Conclusion: Cranial radiotherapy ≥ 20 Gy is associated with an increased prevalence of obesity, especially in females treated at a young age. It is imperative that healthcare professionals recognize this risk and develop strategies to enhance weight control and encourage longitudinal follow-up.

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WITH THE growing recognition of potential long-term health problems related to cancer therapy for childhood cancer, it is essential that risk factors for modifiable disease be identified and addressed. Obesity has been identified as a potential late effect of therapy in survivors of acute lymphoblastic leukemia (ALL).¹⁻¹³ Obesity in childhood, adolescence, and young adulthood is an important predictor of eventual development of adult-onset diabetes mellitus, hypertension, dyslipidemia, and ultimately, cardiovascular disease.¹⁴ Even modest weight gain from age 20 years is strongly associated with an increased risk of coronary heart disease.¹⁵ Population-based studies indicate that more than 75% of hypertension and more than half of the variance in insulin sensitivity in the general population is accounted for by obesity.¹⁶ The risk of death from all causes, cardiovascular disease, cancer, and other diseases increases throughout the ranges of being overweight or obese in both males and females.^{17,18} Primary and secondary prevention of obesity have been shown to reduce morbidity and mortality related to cardiovascular disease. Thus, efforts should be directed at the identification and aggressive management of populations at risk for developing obesity.

In 1986, Zee et al¹ retrospectively examined medical records of 414 pediatric ALL patients treated at St. Jude Children's Research Hospital and reported an increase in excessive weight gain. Since that time, several studies have replicated the finding that ALL survivors appear to be at risk for becoming overweight or obese by completion of therapy, attainment of final height, and early young adulthood.²⁻¹³ The relationship of different doses of cranial radiotherapy (CRT) or of treatment with prednisone or dexamethasone with excessive weight gain among ALL survivors is unclear; results of prior studies have been inconsistent. Studies to date have generally been limited by small sample sizes, lack of comparison groups, and short duration of follow-up.

The purpose of this study was to use a large, retrospective cohort of young adult survivors of childhood ALL and siblings of childhood cancer survivors to determine whether ALL survivors are at increased risk for obesity, whether this risk is associated with CRT or a chemotherapeutic agent used in the treatment of leukemia, and whether sex and age at diagnosis modify the risk.

PATIENTS AND METHODS

Subject Selection and Contact

The Childhood Cancer Survivor Study (CCSS) is a multi-institutional study (see Appendix) of individuals who survived for 5 or more years after

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treatment for cancer, leukemia, tumor, or similar illness diagnosed during childhood or adolescence. Eligibility criteria for the CCSS cohort included diagnosis of leukemia, CNS tumors, Hodgkin's disease, non-Hodgkin's lymphoma, kidney tumor, neuroblastoma, soft tissue sarcoma, or bone tumor; diagnosis and initial treatment at one of the 25 collaborating CCSS institutions; diagnosis date between January 1, 1970, and December 31, 1986; age less than 21 years at diagnosis; and survival 5 years from diagnosis.

The CCSS protocol and contact documents were reviewed and approved by the Human Subjects Committee at each participating institution. Baseline data were collected from members of the study cohort using a 24-page questionnaire. The baseline questionnaire was designed to capture a wide range of information including demographic characteristics, education, income, employment, insurance coverage, marital status, health habits, family history, access and utilization of medical care, medication use, frequency of diagnosed medical conditions among the group, surgical procedures, recurrent cancer, subsequent new neoplasms, and offspring or pregnancy history. Respondents were asked to record their current height and weight without shoes. Additional details regarding the methodology and cohort characteristics were published previously.¹⁹

Cancer Treatment Information

Information about the original cancer diagnosis was obtained for all eligible patients from the treating institution. For all CCSS participants who returned a signed medical release, information about primary cancer therapy was collected, including initial treatment, treatment for relapse, and preparatory regimens for bone marrow transplantation (if applicable). Qualitative information was abstracted from the medical record for 42 specific chemotherapeutic agents, for which quantitative information was abstracted on 22 agents. Copies of radiation therapy records were obtained and centrally reviewed, including dose of cranial and craniospinal radiotherapy and total-body irradiation. The baseline questionnaire and the treatment abstraction form used in data collection are available for review and downloading at www.cancer.umn.edu/ccss.

ALL Survivors and Sibling Comparison Group

A total of 5,854 5-year survivors of ALL were eligible for participation in CCSS. Of these eligible subjects, 783 (13.4%) declined participation, 805 (13.8%) could not be located after extensive tracing efforts and were considered lost to follow-up, and 33 were pending contact. This report is based on data available as of November 2000. Of an available sample size of 2,447 ALL survivors who were alive and 18 years of age or older at time of completion of questionnaire, 594 were still awaiting complete treatment records and 88 were missing anthropometric data. Thus, at the time of analysis, complete treatment data and heights and weights were available for 1,765 survivors of childhood ALL who were 18 years or older.

The demographics and cancer treatment of the 1,765 adult survivors of childhood ALL are provided in Table 1. The mean age at time of interview was 24.1 years (range, 18 to 42 years). The mean age at cancer diagnosis was 7.5 years (range, 0.1 to 20.8 years), with a mean interval from diagnosis to completion of questionnaire of 17.1 years (range, 7.4 to 27.5 years). Forty-nine percent were female and 89.8% were white, non-Hispanics. The sex, age at time of interview, and age at diagnosis of the patients were not significantly different between survivors with missing treatment or anthropometric data ($n = 682$) and those with available data ($n = 1,765$). However, minority survivors were more likely to have incomplete treatment and anthropometric data (40.1%) in comparison with white, non-Hispanic survivors (20.9%; $P < .0001$).

A cohort of sibling controls was assembled by mailing questionnaires to the nearest-age living sibling of a random sample of half of the total (all cancers) CCSS cohort. A total of 2,565 adult siblings were available for comparison with the ALL survivors. Their mean age (29.0 years) was older than that of the ALL survivors. There also were more females (52.9%) and white, non-Hispanics (92.5%).

Outcome Measures

Body-mass index (BMI; kilograms per square meter), calculated from the self-reported height and weights for ALL survivors and siblings of childhood

Table 1. Demographics of Adult Survivors of Childhood Acute Lymphoblastic Leukemia and Siblings of Childhood Cancer Survivors

Variable	ALL Survivors n = 1765	Siblings n = 2565	P
Age at interview, years			
Mean	24.1	29.0	< .001
SD	4.9	7.3	
Median	23.0	28.0	
Range	18-42	18-56	
Sex, % female	49.3	52.9	< .01
Ethnicity, %			
White, NH	89.8	92.5	< .05
Black, NH	5.0	3.0	
Hispanic/Latino	2.4	2.1	
Other	2.8	2.4	
Age at cancer diagnosis, years			
Mean	7.5		
SD	4.5		
Median	6.3		
Range	0.1-20.8		
Interval from diagnosis, years			
Mean	17.1		
SD	4.2		
Median	17.0		
Range	7.4-27.5		
Treatment			
Chemotherapy			
Cytarabine	44.5%		
Cyclophosphamide	45.8%		
Daunorubicin	23.6%		
Dexamethasone	9.8%		
Doxorubicin	27.7%		
L-Asparaginase	89.5%		
Mercaptopurine	93.3%		
Methotrexate	99.7%		
Prednisone	97.6%		
Thioguanine	12.0%		
Vincristine	99.1%		
Etoposide	5.2%		
Chemotherapy without CRT	23.9%		
Chemotherapy with CRT			
10.0-19.9 Gy	28.5%		
20.0-29.9 Gy	43.2%		
≥ 30.0 Gy	4.5%		

NOTE: Percentages are based on the total with available data for each variable. Abbreviations: CRT, cranial radiotherapy; NH, non-Hispanic.

cancer survivors, was used to determine the prevalence of overweight or obese participants. The current National Heart, Lung, and Blood Institute definitions of overweight or obese were used: overweight, BMI, 25-29.9; obese, BMI ≥ 30.0.²⁰ The main outcome variable, a three-level polytomous variable²¹ on the basis of BMI (normal, overweight, obese), was used in the comparison of ALL survivors with siblings.

Analysis

Descriptive univariate analyses were performed to assess the relationship of demographic and treatment variables with BMI and prevalence of overweight or obese participants. Analysis was stratified by sex because of the significant independent effect of this variable on BMI. Because the ALL survivor and sibling cohorts had a small percentage of non-Hispanic black and Hispanic minorities, all minorities were combined into a pooled group and adjusted for in the analysis. Analysis was also adjusted for age at questionnaire completion, whereas age at diagnosis of ALL was evaluated as a possible modifier of treatment effects.

The influence of each chemotherapeutic agent used for ALL was analyzed individually and in combination. Cumulative dosages of CRT were calculated and grouped by 5-Gy intervals from 0 to 50 Gy. A polytomous logistic

Table 2. BMI and Unadjusted Prevalence Rates for Overweight or Obese ALL Survivors and Siblings by Sex

Characteristic	N	BMI		Overweight BMI 25.0-29.9 (%)	Obese BMI ≥ 30 (%)
		Mean	SD		
Males					
Siblings					
Age at study, years					
18-24	399	24.1	4.0	25.6	8.5
25-29	266	26.2	4.4	43.2	15.8
30-34	260	26.6	4.1	48.9	14.6
35+	268	27.3	4.6	44.8	23.5
ALL survivors					
Age at study, years					
18-24	509	24.8	5.0	29.3	13.8
25-29	260	26.2	5.0	36.5	19.6
30-34	93	26.5	5.2	38.7	19.4
35+	33	29.1	5.1	54.6	30.3
Age at diagnosis, years					
0-4	334	25.0	5.0	28.4	15.9
5-9	309	25.8	5.5	32.7	18.1
10-14	164	26.4	5.3	39.6	18.9
15-21	88	25.2	3.9	42.1	10.2
Therapy					
Chemotherapy only	204	25.1	5.2	31.4	14.7
Chemotherapy + CRT 10-19 Gy	269	25.1	4.9	34.9	12.6
Chemotherapy + CRT ≥ 20 Gy	422	26.1	5.2	33.2	20.1
Females					
Siblings					
Age at study, years					
18-24	390	23.1	4.9	14.9	9.5
25-29	334	24.6	5.6	20.1	15.3
30-34	269	25.1	6.2	22.7	15.2
35+	330	25.4	5.6	20.6	20.0
ALL survivors					
Age at study, years					
18-24	520	24.5	5.5	21.5	14.6
25-29	217	25.3	5.9	23.5	18.4
30-34	101	26.0	5.6	23.8	26.7
35+	32	26.2	5.4	21.9	25.0
Age at diagnosis, years					
0-4	338	25.1	5.9	26.0	16.3
5-9	288	25.1	5.6	19.4	19.1
10-14	191	24.6	5.5	18.9	18.3
15-21	53	24.3	4.4	22.6	11.3
Therapy					
Chemotherapy only	217	23.7	5.3	16.6	12.4
Chemotherapy + CRT 10-19 Gy	234	24.0	5.0	20.5	11.5
Chemotherapy + CRT ≥ 20 Gy	419	26.1	5.9	25.8	23.2

Abbreviations: BMI, body-mass index; CRT, cranial radiotherapy; ALL, acute lymphoblastic leukemia.

regression, with the three-level polytomous outcome variable, was used to estimate odds ratios (OR) with 95% confidence intervals (95% CIs) for being overweight or obese rather than being at normal weight in ALL survivors compared with the sibling comparison group.²¹ Age at interview (continuous) and race (categorical) were entered as adjustment variables in assessing the effect of treatment factors. The regression model was fit for each sex separately. To account for potential within-family correlation between the survivor and his or her sibling from the same family, a bootstrap method was used by resampling the family units.²² The statistical inference was based on 1,000 bootstrap iterations in each analysis.

Age at cancer diagnosis was used as an effect-modifier of treatment factors. Because some survivors may have relapsed and received their first radiation treatment several years after diagnosis, age at treatment was also assessed in those who received CRT.

RESULTS

Descriptive statistics of BMI and unadjusted prevalence rates for overweight or obese participants for different demographic and treatment-related variables are presented in Table 2. No chemotherapeutic agent, either individually or in combination, was significantly associated with overweight or obese participants or with an increased BMI in ALL survivors. In ALL survivors treated with chemotherapy only ($n = 421$), adjusted for age and race, no significant association was found with being overweight or obese in comparison with siblings (females, $P = .85$; males, $P = .31$). Similarly, treatment with chemotherapy and CRT of 10 to 19 Gy ($n = 503$) was not associated with an

Table 3. Sex-Specific OR and 95% CI for Overweight or Obese ALL Survivors in Comparison with Siblings, Adjusted for Age and Race

Group	N	Overweight BMI 25.0-29.9			Obese BMI \geq 30		
		OR	95% CI	P	OR	95% CI	P
Males							
Siblings	1,193	1.00	Referent		1.00	Referent	
ALL survivors							
Chemotherapy only, age at diagnosis 0-21	204	1.02	0.71 to 1.43		1.31	0.77 to 2.04	
Chemotherapy + CRT 10-19 Gy, age at diagnosis 0-21	269	1.16	0.85 to 1.60		1.25	0.80 to 1.92	
Chemotherapy + CRT \geq 20 Gy							
Age at diagnosis 0-4	193	0.97	0.64 to 1.41		2.15	1.31 to 3.38	.01
Age at diagnosis 5-9	123	0.96	0.58 to 1.46		1.93	1.07 to 3.28	.05
Age at diagnosis 10-14	76	1.28	0.71 to 2.43		2.02	1.00 to 4.13	.05
Age at diagnosis 15-21	30	0.93	0.40 to 2.19		0.71	0.00 to 1.92	
Females							
Siblings	1,323	1.00	Referent		1.00	Referent	
ALL survivors							
Chemotherapy only, age at diagnosis 0-21	217	1.07	0.70 to 1.59		1.09	0.63 to 1.71	
Chemotherapy + CRT 10-19 Gy, age at diagnosis 0-21	234	1.36	0.93 to 1.97		1.27	0.77 to 1.95	
Chemotherapy + CRT \geq 20 Gy							
Age at diagnosis 0-4	178	3.19	2.07 to 4.82	.001	3.81	2.34 to 5.99	.001
Age at diagnosis 5-9	137	1.28	0.76 to 2.09		2.30	1.39 to 3.59	.01
Age at diagnosis 10-14	81	1.65	0.84 to 2.82		2.16	1.11 to 3.61	.05
Age at diagnosis 15-21	23	1.22	0.27 to 3.43		0.88	0.00 to 2.63	

NOTE: All ages are in years.

Abbreviations: CRT, cranial radiotherapy; OR, odds ratio; CI, confidence interval; BMI, body-mass index; ALL, acute lymphoblastic leukemia.

increased likelihood of being overweight or obese in comparison with siblings (females, $P = .44$; males, $P = .35$).

Higher-dose CRT (20 to 24 Gy) was associated with an increased prevalence of overweight and obese survivors in comparison with siblings. A dose response was not observed with greater increments of CRT, so all categories \geq 20 Gy were collapsed into a single group for analysis. The addition of spinal irradiation to CRT ($n = 167$) was not associated with a further increase in risk for participants being overweight or obese. The age- and race-adjusted OR for obesity in survivors treated with CRT \geq 20 Gy in comparison with siblings was 2.59 for females (95% CI, 1.88 to 3.55; $P < .001$) and 1.86 for males (95% CI, 1.33 to 2.57; $P < .001$). Female survivors were also more likely to be overweight in comparison with siblings (OR, 1.97; 95% CI, 1.44 to 2.65; $P < .001$).

In females, the prevalence of obesity and mean BMI were influenced by age at diagnosis. For females treated with CRT \geq 20 Gy, the age- and race-adjusted BMI was 27.4, 25.8, 24.7, and 23.7 for 0 to 4, 5 to 9, 10 to 14, and 15 to 21 years of age at diagnosis, respectively ($P = .03$). The age- and race-adjusted OR for being obese for females diagnosed at 0 to 4 years of age and treated with CRT \geq 20 Gy was 3.81 (95% CI, 2.34 to 5.99; $P < .001$) in comparison with that of siblings (Table 3). Females diagnosed in mid- to late adolescence (15 to 21 years of age) did not have an increased likelihood of being overweight or obese relative to the siblings. Illustrating the effect of age at diagnosis in females, Fig 1 presents the correlation of BMI (unadjusted for age or race) by age at diagnosis. Only 4% of survivors treated with CRT \geq 20 Gy received their first treatment more than 3 years after diagnosis. There were no significant differences in these findings when age at first treatment with CRT was used instead of age at diagnosis.

The association of age at diagnosis (or treatment) and obesity was not apparent in males. For those treated with CRT \geq 20 Gy,

the age- and race-adjusted BMI was 26.6, 26.9, 26.5, and 24.4 for 0 to 4, 5 to 9, 10 to 14, and 15 to 21 years of age at diagnosis, respectively ($P = .17$). The odds of being obese were significantly increased for males diagnosed in the three younger categories; however, there was not a trend for more significant changes for those age 0 to 4 at diagnosis. Similar to females, males diagnosed at 15 to 21 years of age were not more likely to be obese or overweight in comparison with the siblings.

The interval from cancer diagnosis to age at interview did not modify the outcomes when adjusted for age and race.

DISCUSSION

Although there have been several studies to date about the possible relationship between ALL treatment and subsequent obesity, assessment of risk based on radiation dose, sex, and age at diagnosis has been limited by small sample sizes and lack of optimal comparison groups. This analysis of a large, retrospective cohort of 1,765 adult survivors of childhood ALL with a sibling comparison group firmly establishes that previous treatment with CRT \geq 20 Gy is associated with an increased risk for obesity, particularly for females treated at a younger age. Obesity that develops or extends into the adolescent and young adult years is strongly associated with several common adult health problems, including adult-onset diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, endometrial cancer, and osteoarthritis and may be associated with breast and colon cancer. Recognizing the association between higher-dose CRT (\geq 20 Gy) and obesity is a necessary step to developing targeted surveillance and intervention studies intended to modify risk.

Previous studies¹⁻¹³ have identified an increase in weight gain by the end of therapy and during early follow-up periods in childhood ALL survivors, both in those treated with chemotherapy only and in those also treated with CRT. Four studies of

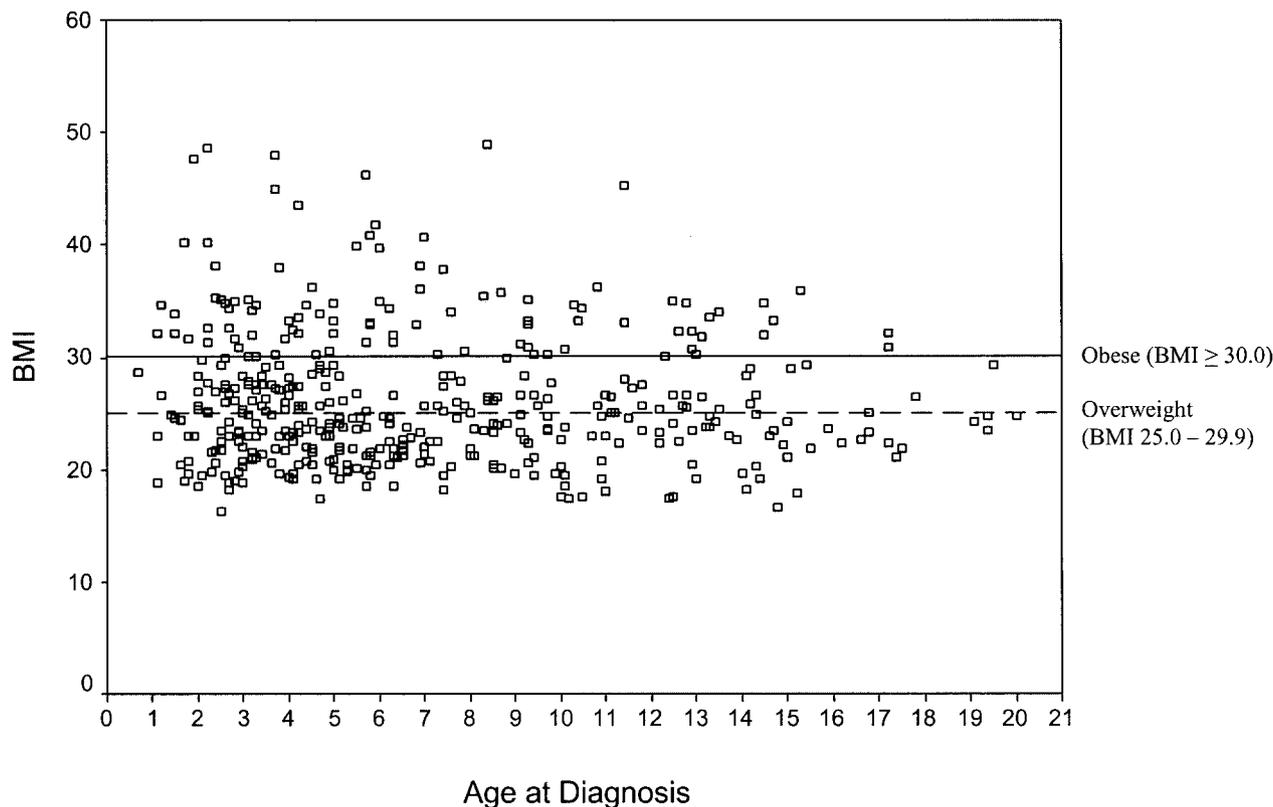


Fig 1. Scatterplot for unadjusted body-mass index (BMI) by age at diagnosis of acute lymphoblastic leukemia for females treated with ≥ 20 Gy cranial radiotherapy.

ALL survivors in the early follow-up period or by time of final height attainment did not find a difference in measures of obesity between those who had been treated with CRT ≥ 20 Gy and those treated with chemotherapy only or lower-dose irradiation.^{4,5,8,10} Craig et al⁷ found an increased risk associated with CRT by final height attainment but reported that this risk was highest for those treated with lower doses (18 to 20 v 22 to 24 Gy). In contrast, Sklar et al¹¹ reported that leukemia survivors treated with either 18 or 24 Gy CRT were more likely to be overweight by final height attainment than those treated with chemotherapy only and that those treated with 24 Gy CRT had the greatest change from prediagnosis weight. The total number of survivors reported in these studies was 1,043: chemotherapy only, $n = 281$; chemotherapy with CRT 10 to 19 Gy, $n = 335$; and chemotherapy with CRT ≥ 20 Gy, $n = 427$. The majority of subjects were less than 18 years of age at time of study.

This CCSS analysis of 1,765 ALL survivors who were 18 years of age or older at time of study included 421 survivors who had received chemotherapy only, 503 survivors who had received CRT 10 to 19 Gy, and 841 survivors who had received CRT ≥ 20 Gy, thus providing an adequate sample size to assess the potential association of CRT with obesity. Females treated with ≥ 20 Gy CRT in this study were 2.6 times more likely to be obese when compared with siblings of cancer survivors, whereas males were 1.8 times as likely to be obese. Not only was sex an important modifying factor, but age at diagnosis also was strongly associated with the risk. Females diagnosed between the ages of 0 and 4 years and treated with ≥ 20 Gy CRT were at high risk, with approximately 55% being overweight or obese. Ad-

justed for age and race, they were almost four times as likely to be obese as the siblings. The older a patient was at diagnosis, the less likely he or she was to be obese in adulthood. In fact, leukemia survivors who were 15 years of age or older at time of diagnosis did not have an increased risk of being overweight or obese, regardless of the radiation dose from CRT.

It is of interest that females exposed to cranial irradiation at a young age tend to be more vulnerable than males and are at increased risk of developing a variety of adverse outcomes in addition to obesity. Neurocognitive impairment,^{23,24} earlier onset of puberty,^{25,26} and reduced final height²⁷ have all been found to occur at higher rates in young females treated with cranial irradiation. Although the pathogenesis of these associations remains unclear, some authors have postulated that this increased vulnerability of the female brain may be related to more rapid brain growth during early childhood in females compared with that in males.²³

Recognizing this strong association of higher-dose CRT and obesity, modified by early age at treatment, it is likely that these findings are secondary to an age-sensitive radiation-induced insult of the pituitary-hypothalamic axis. Two possible mechanisms have been suggested: leptin insensitivity and/or growth hormone deficiency. Radiation at a young age may affect the developing hypothalamus and result in leptin-receptor insensitivity. Leptin is a peptide hormone that is secreted by adipocytes (predominantly white adipose tissue).^{28,29} Circulating leptin levels are proportional to the total fat mass index; thus, the more obese an individual, the higher the leptin level. Leptin stimulates leptin receptors in the ventromedial hypothalamus, resulting in a

decrease in food intake and an increase in energy expenditure. It has been hypothesized that this feedback between leptin, produced by the adipocytes, and the hypothalamus provides a mechanism for the body to sense and respond to alterations in energy balance and act as a satiety signal. Assessing the possible role of leptin-receptor insensitivity in radiation-associated obesity, Brennan et al³⁰ evaluated 32 ALL survivors who had been treated with 18 to 25 Gy CRT (median age 17.8 years) and 35 age- and BMI-matched controls and reported that leptin levels were significantly higher in the leukemia survivors, with an increase in leptin per unit of fat mass. The differences were most marked for those with growth hormone deficiency (GHD; n = 9) and, to a lesser degree, those with insufficient growth hormone peaks (n = 12). Survivors with normal growth hormone stimulation did not have different leptin levels or a difference in leptin to fat mass in comparison with the controls.

Alternatively, the radiation-associated changes may be mediated through alterations in growth hormone secretion. GHD in adulthood is associated with obesity.³¹ Adult survivors of childhood ALL who were treated with CRT are at increased risk for GHD.³² Whether GHD contributes to obesity in survivors is controversial. In an analysis of 50 childhood cancer survivors, including 28 ALL survivors, reduced spontaneous growth hormone secretion was associated with obesity.³³ In contrast, Adan et al³⁴ did not find a significant association between obesity and GHD in an analysis of 90 young adult cancer survivors (28 ALL survivors). It is also plausible that radiation damage to the more radiosensitive hypothalamus^{35,36} may result in both leptin-receptor insensitivity and, in some cases, varying degrees of GH insufficiency.

Importantly, in contrast with a few smaller studies,^{5,7,8} this study did not find a significant association between treatment with chemotherapy only or lower-dose CRT (10 to 19 Gy) and overweight or obese survivors. It is important to note, however, that these previous studies evaluated survivors who were generally in their late childhood or adolescent years and used normative reference values for comparison. In this CCSS study, all participants were at least 18 years of age, with many survivors in their late 20s and early 30s, and they were compared with siblings of childhood cancer survivors. Little data are available that follow changes in BMI from diagnosis of ALL into

adulthood. Thus, whether our findings reflect a normalization of previous weight gain with aging in survivors treated with chemotherapy only cannot be determined from this study.

When interpreting the findings of this study, it is important to recognize several limitations. First, BMI was calculated from self-reported heights and weights, which are subject to a degree of imprecision. However, measurements of weight and height, even those reported by subjects themselves, are generally accurate and do not contribute significantly to errors in assessing BMI.^{37,38} In addition, bias in self-report should be similar for both the leukemia survivors and the sibling comparison groups. Second, a limitation of using BMI as a measure of body fat is that it does not distinguish fat mass from lean mass. More refined methods for estimation of fat mass, including bioimpedance and dual x-ray absorptiometry, may reveal additional risk in ALL survivors treated with chemotherapy only or lower-dose CRT. Nevertheless, BMI is the standard measure of obesity used in population-based studies, and increased BMI is strongly associated with cardiovascular disease, cancer, and all-cause mortality. Third, minority survivors were underrepresented in the sample with complete treatment and anthropometric data, limiting assessment of race and ethnicity as a modifier of outcomes. Finally, this study did not assess risk associated with more recent treatment protocols that include intensified regimens of intravenous methotrexate.

In summary, CRT \geq 20 Gy was associated with an increased prevalence of obesity, especially in females treated during the first few years of life. This cohort is still too young to ascertain the prevalence of obesity-related diseases, such as hypertension, insulin resistance, and dyslipidemia. One can anticipate, however, that without intervention, this therapy-related obesity will lead to significant health risks in this population. Thus, strategies to encourage longitudinal follow-up, periodic surveillance for cardiovascular and other obesity-related risk factors, and interventions to lower risk warrant further study. Additional studies are needed to investigate the possible causation of obesity by radiation at a young age and the mechanism by which this occurs.

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APPENDIX

The appendix is available online at www.jco.org.

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