Obesity in Childhood Cancer Survivors: Call for Early Weight Management[1–3]

Fang Fang Zhang[4,5]* and Susan K Parsons[6–9]

[4]Department of Nutrition Sciences, Friedman School of Nutrition Science and Policy, and [5]Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA; [6]Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA; and Departments of [7]Medicine, [8]Pediatrics, and [9]Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA

ABSTRACT

A high prevalence of obesity and cardiometabolic conditions has been increasingly recognized in childhood cancer survivors. In particular, survivors of pediatric acute lymphoblastic leukemia have been found to be at risk of becoming overweight or obese early in treatment, with increases in weight maintained throughout treatment and beyond. Nutrition plays an important role in the etiology of obesity and cardiometabolic conditions and is among the few modifiable factors that can prevent or delay the early onset of these chronic conditions. However, nutritional intake in childhood cancer survivors has not been adequately examined and the evidence is built on data from small cohorts of survivors. In addition, the long-term impact of cancer diagnosis and treatment on survivors' nutritional intake as well as how survivors' nutritional intake is associated with chronic health conditions have not been well quantified in large-scale studies. Promoting family-based healthy lifestyles, preferably at a sensitive window of unhealthy weight gain, is a priority for preventing the early onset of obesity and cardiometabolic conditions in childhood cancer survivors. *Adv Nutr* 2015;6:611–9.

Keywords: obesity, survivors, childhood cancer, nutrition, lifestyle, intervention

Introduction

Dramatic improvements in the diagnosis and treatment of cancer in childhood have led to a rapidly growing cohort of survivors, now estimated to exceed 420,000 in the United States (1, 2). However, this success has brought the recognition that childhood cancer survivors have an elevated risk of premature mortality and serious morbidity (3–6). Data from the St. Jude's Lifetime Cohort of childhood cancer survivors revealed that, at 45 y of age, the estimated prevalence was 95% for having 1 chronic condition and 80% for having a severe, disabling, or life-threatening condition (3). Notably, childhood cancer survivors are 7 times more likely to die from cardiac causes than the general population (4, 6). They experience a significantly high risk of developing cardiovascular disease (CVD)[10] (7–9) and related factors such as hypertension (10, 11), dyslipidemia (10, 11), insulin resistance or diabetes (10–13), and obesity (14, 15) at a young age. Chronic conditions diagnosed in young adulthood are strong predictors for subsequent mortality (2, 4, 6). Obesity adds additional risks to the elevated chronic health conditions already experienced by childhood cancer survivors. Identifying risk factors for obesity and obesity-related chronic conditions is a major priority for improving the long-term health of childhood cancer survivors. We provide a critical review of the current state of research and knowledge of obesity and associated risk factors in survivors of childhood cancer.

Current Status of Knowledge

Prevalence of obesity in childhood cancer survivors

Although malnutrition due to cancer-related anorexia and cachexia still represents an important concern in cancer

[1] This article is a review from the "Clinical Brief: Nutritional Issues in Childhood Cancer Survivors" session presented at the Advances & Controversies in Clinical Nutrition Conference held 4–6 December 2014 in National Harbor, MD. The conference was jointly provided by the American Society for Nutrition (ASN) and Tufts University School of Medicine. The article is also a review from the "SPLIT C—Childhood Cancer and Survivorship" session presented at the American Institute for Cancer Research (AICR) Conference on Food, Nutrition, Physical Activity, and Cancer held 29–31 October 2014 in Washington, DC.

[2] All phases of this study were supported by Boston Nutrition Obesity Research Center grant P30DK46200, the National Center for Research Resources grant UL1 RR025752, the National Center for Advancing Translational Sciences and NIH grant UL1 TR000073, and the Tufts Collaborates grant.

[3] Author disclosures: FF Zhang and SK Parsons, no conflicts of interests. The funding sources had no role in the design, conduct, or analysis of this study or in the decision to submit the manuscript for publication.

* To whom correspondence should be addressed. E-mail: fang_fang.zhang@tufts.edu.

[10] Abbreviations used: ALL, acute lymphoblastic leukemia; CCSS, Childhood Cancer Survivor Study; COG, Children's Oncology Group; CRT, cranial radiation therapy; CVD, cardiovascular disease; HEI, Healthy Eating Index.

care for survivors of childhood cancer (16), overconsumption of food calories and reduced energy expenditure due to physical inactivity are also apparent. The Childhood Cancer Survivor Study (CCSS), a consortium of 26 pediatric oncology centers in the United States and Canada, assessed the BMI of 1451 adult survivors of acute lymphoblastic leukemia (ALL), the most commonly diagnosed cancer in children and adolescents, and of 2167 same-sex siblings between 1995–1996 and 2002–2003 (17). Findings of this longitudinal study revealed that the prevalence of obesity [defined as BMI (in kg/m^2) $\geq$30] increased in both the survivors and their siblings, but the survivors experienced a greater increase in obesity rate than their siblings (13.5% vs. 7.5%). It should be noted that childhood cancer survivors enrolled in this original cohort of the CCSS were mostly young adults (mean age: 32.3 y) and were long-term survivors (mean interval from diagnosis: 25.1 y) (17).

Increased obesity rates in comparison to the general population have also been reported in many other studies, and these studies tend to vary appreciably by length of survivorship and treatment protocols. For survivors of childhood cancer aged <20 y, the BMI *z* score or percentile is often used to evaluate weight status, rather than the absolute BMI, because an increased BMI is part of normative/adolescent development and also varies by sex (18). The BMI *z* score or percentile can be calculated on the basis of age- and sex-specific mean BMI of a reference population, such as the 2000 CDC growth charts for children aged 2–20 y (19). The BMI *z* score indicates the number of SDs the measurement is away from the age- and sex-specific mean in the reference population, whereas the BMI percentile indicates the position of a child's BMI relative to children of the same sex and age in the reference population. A BMI *z* score >0 indicates a higher-than-average BMI as would a BMI >50th percentile. In our recent meta-analysis, a synthesis of 20 studies over the past 35 y, we identified a mean BMI *z* score of 0.83 in 1743 survivors of childhood ALL. This summary BMI *z* score suggests that young survivors, mostly preteenagers and adolescents who were off-treatment <10 y, had a substantially higher BMI than the reference population. Importantly, obesity is prevalent in young pediatric ALL survivors regardless of receipt of cranial radiation therapy (CRT), sex, and age at diagnosis (15).

Early onset of obesity in childhood cancer survivors

Accumulating evidence suggests that obesity occurs early during survivorship. Recent data from the CCSS suggest that 24-y-old childhood cancer survivors have the same cumulative incidence of severe or disabling, life-threatening, or fatal health conditions as 50-y-old siblings (5). Several longitudinal studies have examined weight patterns in patients with childhood ALL at key time points during and after treatment, such as at diagnosis, at the end of induction, at the end of consolidation, during maintenance, and years after treatment completion. These studies consistently identified a significant increase in the rate of overweight (BMI: 85–94.9th percentile) or obesity (BMI $\geq$95th percentile) during treatment. For example, in a retrospective cohort of 83 patients with childhood ALL diagnosed between 1985 and 2010, our research team found the percentage of being overweight or obese increased from 20% at diagnosis to ~40% at the end of treatment (**Figure 1**) (20). In 183 patients with childhood ALL, Esbenshade et al. (21) similarly reported an increase in the overweight/obesity rate from 36% at diagnosis to 49% at the end of treatment; and the study by Withycombe et al. (22) in 1017 patients with high-risk ALL from the Children's Oncology Group (COG) found an increase in the overweight/obesity rate from 27% at diagnosis to 42% at the end of treatment. The most recent data from 269 standard-risk patients with ALL treated without CRT in COG also detected an increase in overweight/obesity rate from 14% at diagnosis to 39% at the end of therapy (23). The prevalence of overweight/obesity in pediatric patients with ALL at the end of treatment (39–40%) appears to be higher than the prevalence in the general population, which ranged between 33% and 34% in 6395 children and adolescents aged 6–19 y in the 2003–2006 NHANES (24). And these studies all observed a rapid weight gain during the induction and early maintenance cycles of the treatment (20, 21, 23, 25).

To further describe the trajectory of weight changes during treatment, we recently completed a meta-analysis from

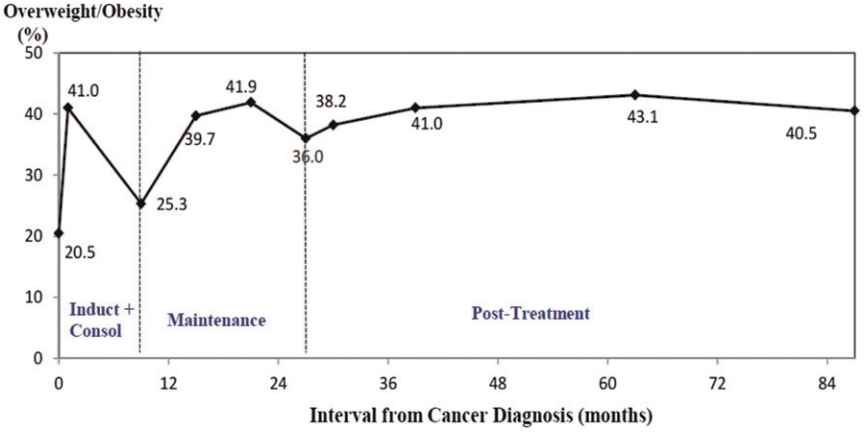

FIGURE 1 Changes in prevalence of overweight and obesity during and after treatment in childhood ALL survivors. Values are prevalences (%), n = 83. Reproduced from reference 20 with permission. © 2014 Wiley Periodicals, Inc. ALL, acute lymphoblastic leukemia; Consol, consolidation; Induct, induction.

21 studies that assessed the longitudinal trend of BMI *z* score (26). The results supported the notion that pediatric patients with ALL gained substantial weight during early treatment (i.e., from diagnosis to start of maintenance) and again during maintenance. Overall, the mean increase in BMI *z* score during treatment was 0.8 in 1514 pediatric patients with ALL (**Figure 2**). To illustrate this, consider a 5-y-old boy with an average BMI (i.e., BMI *z* score = 0 or BMI = 50th percentile) at diagnosis; by the end of treatment at age 7–8 y, this increase corresponds to 4 pounds (1.8 kg) of extra weight gain, compared with his peers, assuming normal growth in height. These findings provide strong support that the treatment phase is a sensitive window for unhealthy weight gain and potentially obesity-related cardiometabolic abnormalities in pediatric patients with ALL.

Importantly, in our meta-analysis, pediatric patients with ALL did not return to their pretreatment weight and were consistently more overweight or obese than their noncancer peers beyond treatment completion. From diagnosis to several years after treatment completion, the mean increase in BMI *z* score remained high, ranging from 0.5 to 0.9 (Figure 2) (26). Although studies with a longer length of follow-up are required to further evaluate the obesity rate in long-term survivors, the existing literature suggests that the unhealthy weight gain that occurred early in treatment is unlikely to be reversed after children complete cancer treatment (26).

Predictors for obesity in childhood cancer survivors

Weight gain is generally considered as a consequence of positive energy balance (i.e., amounts of energy intake exceed amounts of energy expenditure). There is a growing body of evidence suggesting that childhood cancer survivors have high energy intakes due to overconsumption of foods with high energy density and corresponding low expenditure due to sedentary lifestyles.

Nutritional intake. The nutritional intake in childhood cancer survivors has not been adequately examined, and the existing evidence has mostly featured small cohorts of survivors. Some studies examined the adherence of survivors' diet to the current dietary guidelines (27–31). Although different diet quality indices and assessment methods were used to capture dietary intake, existing studies all reported poor diet quality in childhood cancer survivors (27–29, 32, 33). The mean diet quality score was either less than half (28) or only slightly above half (27, 29, 32, 33) of the maximum score, ranging from 33% to 56%. For example, we found that the mean Healthy Eating Index (HEI)–2010 score was 52.7 in 22 childhood leukemia or lymphoma survivors (33), a value that is similar to the mean HEI-2005 of 55.5, which was previously reported in 91 childhood cancer survivors (27). The HEI measures the adherence to the Dietary Guidelines for Americans, with a maximum score of 100 (34). A higher HEI indicates a better diet quality. Overall, childhood cancer survivors showed a low percentage of consuming ≥5 servings of vegetables and fruits each day (27, 29, 32, 35). In particular, survivors had a low adherence to consumption of green vegetables (27), and the actual intake relative to the recommended intake was <50% (28, 29). Survivors also were found to consume fewer whole grains (30) and dietary fiber (28, 29, 33), but they derive a higher percentage of calories from fat (28, 30, 35), saturated fat (27, 28), and refined carbohydrates (35) compared with the recommended intake. One study reported that childhood cancer survivors consumed 10% more total calories than estimated energy requirements (36). On the other hand, childhood cancer survivors had a good adherence to the recommended intakes of dairy or milk (27, 28) and total-protein foods or meat and beans (27, 28), although the adherence to seafood and plant protein recommendations remained poor (33).

Few studies have assessed the dietary intake of a broad category of micronutrients and minerals in childhood cancer survivors. One obstacle for studying nutritional intake is the lack of a valid method to quantify habitual intake. Two common methods used to assess diet are FFQs and repeated 24-h dietary recalls (37). FFQs are designed to measure a person's typical diet over a defined period of time, and 24-h dietary recalls involve a recall of food intake in the preceding 24 h (37). The use of FFQs has been associated with substantial underreporting of dietary intake and therefore is not appropriate to estimate absolute intakes of nutrients and minerals (38, 39). Repeated 24-h dietary recalls, on the other hand, provide more valid estimates and are often used as the reference method to validate FFQs (40). Using repeated 24-h dietary recalls over 12 mo, we observed a low intake of vitamin D and calcium in 22 childhood cancer survivors (33). Only 4% of the survivors met the recommended intake

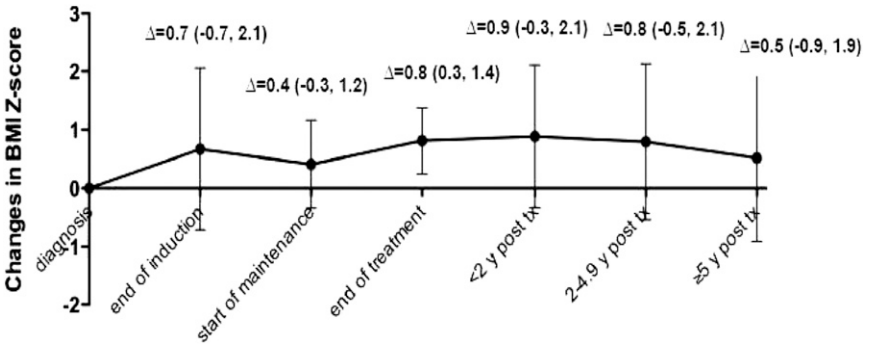

FIGURE 2 Changes in BMI *z* score from diagnosis in childhood ALL survivors: a meta-analysis. Values are means (95% CIs), *n* = 1514. ALL, acute lymphoblastic leukemia; tx, treatment. Reproduced from reference 26 with permission. © 2015 Wiley Periodicals, Inc.

for vitamin D, whereas 29% met the recommended intake for calcium (33). Cohen et al. (36), using 3-d food records to assess dietary intake in 50 childhood cancer survivors, found that 32% of the survivors did not meet the recommended intake for calcium. A high percentage of childhood cancer survivors were found not to meet the recommended intake for folate and iron (50% and 44%, respectively) (36). We also found a very low adherence to recommended potassium intake, which may be explained by low consumptions of vegetables and fruits (33). In contrast, existing studies consistently reported a high sodium intake in childhood cancer (27, 28, 32, 33), with a mean sodium intake >3000 mg/d, although the upper limit is 2300 mg/d in the 2010 Dietary Guidelines (34).

Little is known about whether childhood cancer survivors' dietary intake differs from that of the general population. The only study that compared dietary intake of childhood cancer survivors with that of siblings did not find that the HEI-2005 and its 12 components differed significantly between the 91 survivors and 30 siblings (27). Poor nutritional intake can significantly exacerbate chronic health conditions experienced by the survivors, who are at higher risk of developing these conditions at a much younger age than the general population (5).

Physical activity. A substantial number of studies assessed physical activity level in childhood cancer survivors, including several publications from the CCSS in which self-reported physical activity was assessed by using adapted questions from the Behavior Risk Factor Surveillance System (41–49). Two CCSS studies reported that survivors were 60–70% more likely to be physically inactive than their siblings (47) or healthy controls (44). Overall, various reports from the CCSS found that ~50–70% of survivors of childhood cancer did not meet the CDC guidelines for physical activity, although definitions of meeting the physical activity guidelines varied across studies. Other studies involving other patient cohorts have shown similar patterns of reduced physical activity in childhood cancer survivors (32, 50, 51). When accelerometers were used to objectively measure levels of physical activity in 1 study, <5% of childhood cancer survivors met the CDC guidelines for physical activity (51). Studies that assessed levels of physical activity in adolescent (11–18 y) and younger adult (19–25 y) survivors of childhood cancer on the basis of self-report (35, 52–64) also observed that a substantial proportion of the adolescent and younger adult survivors, ranging between 50% and 80%, did not adhere to CDC guidelines for physical activity (35, 52, 58, 61, 63, 64). Adolescents experience the steepest decline in physical activity across all age groups (65). However, because methods used to assess physical activity vary substantially in existing studies, it cannot be directly determined whether the poor adherence to physical activity guidelines in adolescent survivors is similar to that reported for the general adolescent population, such as in NHANES (66, 67).

Studies that compared levels of physical activity in childhood cancer survivors with those without cancer reported varying results. Although some reports suggested that survivors are less active (56, 62, 68), others reported the opposite or no difference (60, 69). However, when the longitudinal trend of physical activity levels was evaluated, a significant decline in physical activity during treatment was reported in 97 adolescent survivors (age range: 15–20 y) who were asked to recall levels of physical activity during and after treatment. The proportion who were physically inactive increased from 26.4% at diagnosis to 84.5% at the end of treatment and persisted beyond treatment completion (54, 55).

A few studies provided empirical evidence on the levels of total energy expenditure in childhood cancer survivors. Our study (70) and the study by Reilly et al. (71) assessed total energy expenditure in childhood cancer survivors using the doubly labeled water method. The doubly labeled water method provides an accurate and objective assessment on energy expenditure in free-living individuals and is considered as the reference method to measure total energy expenditure (72, 73). In 17 childhood cancer survivors (median age: 11.5 y), we found a mean total energy expenditure of 2173 kcal/d (70), similar to the mean energy expenditure of 2150 kcal/d in 20 childhood cancer survivors (mean age: 10.9 y) (71). Importantly, childhood cancer survivors have an energy deficit of nearly 500 kcal/d compared with the estimated energy requirement for the recommended level of physical activity (70). This energy gap could be partially addressed by promoting an average of 60 min/d of moderate-to-vigorous physical activity such as brisk walking and swimming (~250–400 kcal/d). However, physical activity alone may be insufficient to reverse an energy gap of 500 kcal/d. Dietary modification to facilitate a reduction in energy intake may also be needed to achieve energy balance in childhood cancer survivors.

Mechanisms for obesity and CVD risk in childhood cancer survivors

Although poor dietary intake and sedentary behaviors can be fueled by the "obesogenic" environment to which the entire society is exposed, childhood cancer survivors have a unique factor that may put them at a higher risk of obesity than their peers—that is, the cancer treatment received at a very young age. Cancer and its treatment can affect obesity and CVD risk through complex pathways (**Figure 3**). Several regimens for treating hematologic malignancies include corticosteroids. Corticosteroids are known to be critically involved in regulating energy intake, storage, and mobilization. The prolonged use of corticosteroids has shown effects on body composition associated with increases in percentage of body fat in pediatric ALL survivors (74). Two studies in patients with ALL receiving maintenance therapy reported a significant increase in caloric intake while patients were receiving corticosteroids (75, 76). Results from animal studies also provide compelling evidence that passive elevation in glucocorticoids provokes a dose-response increase in energy intake—in particular, a proportional increase in the intake of calories from high-energy-dense foods (77). Although

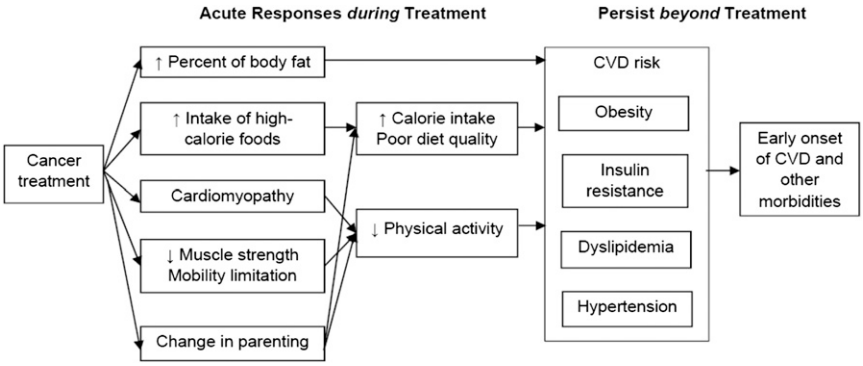

FIGURE 3 A conceptual model of obesity and CVD risk in childhood cancer survivors. CVD, cardiovascular disease.

patterns of dietary intake were originally thought to be acute responses to cancer treatment, recent evidence indicates that children had difficulty reversing unhealthy eating habits after treatment completion (78), and a high proportion of childhood cancer survivors report taste preferences that interfere with adherence to a low-fat diet (79).

CRT is a common treatment for brain tumors and is used in selected leukemia regimens to prevent central nervous system relapse. CRT can directly damage the hypothalamic-pituitary region, impairing signaling reception from hormones such as ghrelin and leptin that regulate hunger and appetite (14, 80–82). These findings suggest that cancer treatment may have a long-lasting impact on survivors' diet. Nevertheless, whether survivors' nutritional intake patterns are associated with patient and treatment characteristics has not been well quantified. We previously found that that long-term survivors (time from diagnosis: ≥10 y) had a lower diet quality than more recent survivors (time from diagnosis: <5 y) (33), and another study (27) found that childhood cancer survivors treated with CRT had a lower diet quality than those treated without CRT. However, both studies were based on small cohorts of survivors. Large-scale studies with systematic assessments on patient and treatment characteristics are required to further quantify the impact of cancer diagnosis and treatment on nutritional intake in childhood cancer survivors.

Cancer treatment can also directly affect the levels of physical activity in childhood cancer survivors. Receipt of CRT may decrease muscle mass and strength and impair balance and postural control (44). Anthracyclines and thoracic radiation, used in treating selected youth with cancer, have been known to cause left ventricular dysfunction and subsequent impairment in cardiovascular fitness (8). Vincristine, used in all phases of ALL treatment, is an established risk factor for neuropathy, which often results in reduced muscle strength, impaired balance, and other mobility limitations. These physical impairments can lead to reduced physical activity in childhood cancer survivors (58). In addition to contributing to obesity risk through causing positive energy balance, some chemotherapeutic drugs such as L-asparaginase (83–85) and prednisone (86) can directly impair β cell function and lipid synthesis, leading to hyperinsulinemia and dyslipidemia. Obesity and cardiometabolic conditions can further contribute to serious morbidity and premature mortality in childhood cancer survivors.

Family environment also plays an important role in shaping children's dietary and activity behaviors (87). Family factors and parental control can be particularly important for children diagnosed with cancer at a young age. In response to the impact of the disease and treatment complexity, parents may be permissive on issues such as diet and physical activity while the child is undergoing cancer treatment. After the completion of treatment, parents find difficulties in reversing the unhealthy eating habits and sedentary lifestyle that have been established during cancer treatment (78). Taken together, treatment-induced positive energy balance and metabolic abnormalities, coupled with negative behavioral adaptions that occur early in treatment, tend to persist beyond treatment completion and may cause early onset of obesity and CVD risk in childhood cancer survivors (Figure 3).

Lifestyles and chronic health conditions in childhood cancer survivors

Many established CVD risk factors in the general population are preventable or modifiable (88). Nutrition and physical activity play important roles in the etiology of chronic health conditions and are among the few modifiable behaviors that can prevent or delay the early onset of chronic diseases. Although intervention studies have provided strong evidence that behavioral modifications reduce CVD risk factors and events in the general population, few studies have examined nutrition, physical activity, and chronic health conditions in childhood cancer survivors. Studies that evaluated nutritional intake in association with obesity and cardiometabolic conditions reported inconsistent findings (27–30). Among the few studies that assessed physical activity with chronic health conditions, 1 large cross-sectional study from the CCSS reported a 10% increased prevalence of obesity in association with low levels of vigorous physical activity (<30 min/d for at least 3 d/wk) (45), and 2 studies reported that low levels of physical activity were associated with low bone mineral density (60, 62).

Conclusions

Childhood cancer survivors have a significantly elevated risk of obesity and cardiometabolic conditions. Poor dietary

intake patterns and low levels of physical activity can both contribute to obesity and CVD risk in this population. Although treatment exposures alone or in combination also contribute to elevated cardiometabolic risk in childhood cancer survivors, it is important to note that the attributable fraction identified in 1713 adult survivors of childhood cancer was <50%, ranging from 9.3% for hypertension to 15.5% for dyslipidemia, 41.7% for diabetes, and 42.1% for obesity (3). This leaves ample room for improvement through behavioral interventions. Therefore, it is critical to further improve our understanding of the lifestyle behaviors in childhood cancer survivors, especially for dietary intake patterns for which few data from large-scale cohorts exist. Although dietary guidelines have been developed for cancer survivors, such as those developed by the American Cancer Society (89) and the World Cancer Research Fund/American Institute for Cancer Research (90), these guidelines focus on survivors with malignancies other than childhood cancer. The long-term follow-up guidelines for childhood cancer survivors, developed by the COG, do not have a specific focus on nutrition (91). The lack of specific dietary guidelines for childhood cancer survivors may be explained by the fact that the nutritional intake and its associations with chronic health conditions are still poorly understood in this population. Improvement of our knowledge of nutritional intake in childhood cancer survivors is critical to developing evidence-based dietary recommendations for this population. In addition, little knowledge exists for the association between diet, physical activity, and chronic health conditions in childhood cancer survivors and, in particular, to determine whether survivors who had specific treatment exposure experience differential associations for nutrition and chronic health outcomes compared with those who are not at risk. Existing studies have focused primarily on survivors of pediatric ALL; and we know very little about the impact of other cancer diagnoses, age at diagnosis, and time from diagnosis on lifestyle and chronic health conditions in childhood cancer survivors. Large-scale studies with systematic assessments on patient and treatment characteristics are required to further quantify the impact of nutritional intake by cancer- and treatment-related characteristics so that targeted recommendations can be made to improve diet quality in this population.

Cancer diagnosis may serve as a "teachable moment" and trigger positive lifestyle changes in the survivors. Few interventions are designed to promote lifestyle modifications in this population, in particular in young survivors who are at a sensitive window of unhealthy weight gain and development of modifiable CVD risk factors. Many programs for cancer treatment and survivorship care do not include weight management. This disparity has been recognized by the Institute of Medicine in its 2013 workshop summary outlining recommendations for improving the care and outcomes for adolescent children with cancer (92). In particular, an increasing body of evidence now suggests that unhealthy weight gain and the development of CVD risk factors occur early in treatment and persist beyond treatment completion. If the intervention is initiated late in survivorship (78), reversing the unhealthy eating habits and sedentary lifestyle established during treatment may become difficult.

Family environment plays a highly influential role in shaping children's diet and activity behaviors (87), in particular for younger children (3–11 y old) given their limited autonomy and dependence on adult caregivers. For families with children who have survived cancer, family environment can be even more important because a close parent-child relationship is often expected (52). Previous research provides convincing evidence that interventions targeting parents exclusively or targeting parents and children together yield greater success in preventing childhood obesity than those targeting children alone (93–95). Therefore, weight-management programs in young childhood cancer survivors need to engage parents as the "agents of change," emphasizing parents' roles in transitioning the family toward healthy eating and exercise through modifying both physical and social family environment, and help parents resume a more authoritative role with parenting after a child's diagnosis and treatment of cancer. Promoting family-based healthy lifestyles, preferably at a sensitive window of unhealthy weight gain, is becoming a priority for preventing the early onset of CVD risk factors in childhood cancer survivors.

Acknowledgments

Both authors read and approved the final manuscript.

References

1. Mariotto AB, Rowland JH, Yabroff KR, Scoppa S, Hachey M, Ries L, Feuer EJ. Long-term survivors of childhood cancers in the United States. Cancer Epidemiol Biomarkers Prev 2009;18:1033–40.
2. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nat Rev Cancer 2014;14:61–70.
3. Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, Green DM, Armstrong GT, Nottage KA, Jones KE, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 2013;309:2371–81.
4. Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL, Mertens AC. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol 2009;27:2328–38.
5. Armstrong GT, Kawashima T, Leisenring W, Stratton K, Stovall M, Hudson MM, Sklar CA, Robison LL, Oeffinger KC. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. J Clin Oncol 2014;32:1218–27.
6. Mertens AC, Liu Q, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT, Robison LL, Yasui Y. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2008;100:1368–79.
7. Rugbjerg K, Mellemkjaer L, Boice JD, Kober L, Ewertz M, Olsen JH. Cardiovascular disease in survivors of adolescent and young adult cancer: a Danish cohort study, 1943–2009. J Natl Cancer Inst 2014;106:dju110.
8. Oeffinger KC. Are survivors of acute lymphoblastic leukemia (ALL) at increased risk of cardiovascular disease? Pediatr Blood Cancer 2008;50(2, Suppl):462–7.
9. Bowers DC, Liu Y, Leisenring W, McNeil E, Stovall M, Gurney JG, Robison LL, Packer RJ, Oeffinger KC. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2006;24:5277–82.

10. Meacham LR, Chow EJ, Ness KK, Kamdar KY, Chen Y, Yasui Y, Oeffinger KC, Sklar CA, Robison LL, Mertens AC. Cardiovascular risk factors in adult survivors of pediatric cancer—a report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev 2010;19:170–81.
11. Nottage KA, Ness KK, Li C, Srivastava D, Robison LL, Hudson MM. Metabolic syndrome and cardiovascular risk among long-term survivors of acute lymphoblastic leukaemia—from the St. Jude Lifetime Cohort. Br J Haematol 2014;165:364–74.
12. Meacham LR, Sklar CA, Li S, Liu Q, Gimpel N, Yasui Y, Whitton JA, Stovall M, Robison LL, Oeffinger KC. Diabetes mellitus in long-term survivors of childhood cancer: increased risk associated with radiation therapy: a report for the childhood cancer survivor study. Arch Intern Med 2009;169:1381–8.
13. Oeffinger KC, Adams-Huet B, Victor RG, Church TS, Snell PG, Dunn AL, Eshelman-Kent DA, Ross R, Janiszewski PM, Turoff AJ, et al. Insulin resistance and risk factors for cardiovascular disease in young adult survivors of childhood acute lymphoblastic leukemia. J Clin Oncol 2009;27:3698–704.
14. Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, Vik TA, Inskip PD, Robison LL. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2003;21:1359–65.
15. Zhang FF, Kelly MJ, Saltzman E, Must A, Roberts SB, Parsons SK. Obesity in pediatric ALL survivors: a meta-analysis. Pediatrics 2014;133:704–15.
16. Bauer J, Jurgens H, Fruhwald MC. Important aspects of nutrition in children with cancer. Adv Nutr 2011;2(2):67–77.
17. Garmey EG, Liu Q, Sklar CA, Meacham LR, Mertens AC, Stovall MA, Yasui Y, Robison LL, Oeffinger KC. Longitudinal changes in obesity and body mass index among adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2008;26:4639–45.
18. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics 2007;120(Suppl 4):S164–92.
19. Centers for Disease Control and Prevention. [Internet] Atlanta (GA): National Center for Health Statistics. CDC growth charts. c May 30, 2000 [cited 2015 Feb 15]. Available from: http://www.cdc.gov/growthcharts/.
20. Zhang FF, Rodday AM, Kelly MJ, Must A, Macpherson C, Roberts SB, Saltzman E, Parsons SK. Predictors of being overweight or obese in survivors of pediatric acute lymphoblastic leukemia (ALL). Pediatr Blood Cancer 2014;61:1263–9.
21. Esbenshade AJ, Simmons JH, Koyama T, Koehler E, Whitlock JA, Friedman DL. Body mass index and blood pressure changes over the course of treatment of pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer 2011; 56:372–8.
22. Withycombe JS, Smith LM, Meza JL, Merkle C, Faulkner MS, Ritter L, Seibel NL, Moore K. Weight change during childhood acute lymphoblastic leukemia induction therapy predicts obesity: a report from the Children's Oncology Group. Pediatr Blood Cancer 2015;62:434–9.
23. Lindemulder SJ, Stork LC, Bostrom B, Lu X, Devidas M, Hunger S, Neglia JP, Kadan-Lottick NS. Survivors of standard risk acute lymphoblastic leukemia do not have increased risk for overweight and obesity compared to non-cancer peers: a report from the Children's Oncology Group. Pediatr Blood Cancer 2015;62:1035–41.
24. Ogden CL, Carroll MD, Flegal KM. High body mass index for age among US children and adolescents, 2003–2006. JAMA 2008;299:2401–5.
25. Withycombe JS, Post-White JE, Meza JL, Hawks RG, Smith LM, Sacks N, Seibel NL. Weight patterns in children with higher risk ALL: a report from the Children's Oncology Group (COG) for CCG 1961. Pediatr Blood Cancer 2009;53:1249–54.
26. Zhang FF, Liu SS, Chung M, Kelly MJ. Growth patterns of pediatric ALL patients during and after treatment. Pediatr Blood Cancer. 2015 Mar 24 (ePub ahead of print; DOI: 10.1002/pbc.25519).
27. Landy DC, Lipsitz SR, Kurtz JM, Hinkle AS, Constine LS, Adams MJ, Lipshultz SE, Miller TL. Dietary quality, caloric intake, and adiposity of childhood cancer survivors and their siblings: an analysis from the cardiac risk factors in Childhood Cancer Survivors Study. Nutr Cancer 2013;65:547–55.
28. Robien K, Ness KK, Klesges LM, Baker KS, Gurney JG. Poor adherence to dietary guidelines among adult survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2008;30:815–22.
29. Tonorezos ES, Robien K, Eshelman-Kent D, Moskowitz CS, Church TS, Ross R, Oeffinger KC. Contribution of diet and physical activity to metabolic parameters among survivors of childhood leukemia. Cancer Causes Control 2013;24:313–21.
30. Tylavsky FA, Smith K, Surprise H, Garland S, Yan X, McCammon E, Hudson MM, Pui CH, Kaste SC. Nutritional intake of long-term survivors of childhood acute lymphoblastic leukemia: evidence for bone health interventional opportunities. Pediatr Blood Cancer 2010; 55:1362–9.
31. Zhang FF, Saltzman E, Must A, Parsons SK. Do childhood cancer survivors meet the diet and physical activity guidlines? A review of guidelines and literature. Int J Child Health Nutr 2012;1:44–58.
32. Smith WA, Li C, Nottage KA, Mulrooney DA, Armstrong GT, Lanctot JQ, Chemaitilly W, Laver JH, Srivastava DK, Robison LL, et al. Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. Cancer 2014;120:2742–50.
33. Zhang FF, Saltzman E, Kelly MJ, Liu S, Must A, Parsons SK, Roberts SB. Comparison of childhood cancer survivors' nutritional intake with US dietary guidelines. Pediatr Blood Cancer 2015; Mar 24 (ePub ahead of print; DOI: 10.1002/pbc.25521).
34. US Department of Agriculture. Dietary guidelines for Americans. 7th ed. Washington (DC): USDA; 2010.
35. Demark-Wahnefried W, Werner C, Clipp EC, Guill AB, Bonner M, Jones LW, Rosoff PM. Survivors of childhood cancer and their guardians. Cancer 2005;103:2171–80.
36. Cohen J, Wakefield CE, Fleming CA, Gawthorne R, Tapsell LC, Cohn RJ. Dietary intake after treatment in child cancer survivors. Pediatr Blood Cancer 2012;58:752–7.
37. Willett WC, editor. Nutritional epidemiology. New York: Oxford University Press; 1998.
38. Livingstone MB, Robson PJ, Wallace JM. Issues in dietary intake assessment of children and adolescents. Br J Nutr 2004;92(Suppl 2):S213–22.
39. Livingstone MB, Black AE. Markers of the validity of reported energy intake. J Nutr 2003;133(Suppl 3):895S–920S.
40. Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, McIntosh A, Rosenfeld S. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. Am J Epidemiol 2001;154:1089–99.
41. Butterfield RM, Park ER, Puleo E, Mertens A, Gritz ER, Li FP, Emmons K. Multiple risk behaviors among smokers in the Childhood Cancer Survivors Study cohort. Psychooncology 2004;13:619–29.
42. Castellino SM, Casillas J, Hudson MM, Mertens AC, Whitton J, Brooks SL, Zeltzer LK, Ablin A, Castleberry R, Hobbie W, et al. Minority adult survivors of childhood cancer: a comparison of long-term outcomes, health care utilization, and health-related behaviors from the Childhood Cancer Survivor Study. J Clin Oncol 2005;23:6499–507.
43. Cox CL, Montgomery M, Oeffinger KC, Leisenring W, Zeltzer L, Whitton JA, Mertens AC, Hudson MM, Robison LL. Promoting physical activity in childhood cancer survivors: results from the Childhood Cancer Survivor Study. Cancer 2009;115:642–54.
44. Florin TA, Fryer GE, Miyoshi T, Weitzman M, Mertens AC, Hudson MM, Sklar CA, Emmons K, Hinkle A, Whitton J, et al. Physical inactivity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev 2007;16:1356–63.
45. Green DM, Cox CL, Zhu L, Krull KR, Srivastava DK, Stovall M, Nolan VG, Ness KK, Donaldson SS, Oeffinger KC, et al. Risk factors for obesity in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2012;30:246–55.
46. Krull KR, Annett RD, Pan Z, Ness KK, Nathan PC, Srivastava DK, Stovall M, Robison LL, Hudson MM. Neurocognitive functioning and health-related behaviours in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Eur J Cancer 2011;47 (9):1380–8.

47. Ness KK, Leisenring WM, Huang S, Hudson MM, Gurney JG, Whelan K, Hobbie WL, Armstrong GT, Robison LL, Oeffinger KC. Predictors of inactive lifestyle among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 2009;115:1984–94.
48. Wampler MA, Galantino ML, Huang S, Gilchrist LS, Marchese VG, Morris GS, Scalzitti DA, Hudson MM, Oeffinger KC, Stovall M, et al. Physical activity among adult survivors of childhood lower-extremity sarcoma. J Cancer Surviv 2012;6:45–53.
49. Center for Disease Control and Prevention. Physical activity guidelines [cited 2014 Oct 1]. Available from: http://www.health.gov/paguidelines/.
50. Phillips-Salimi CR, Lommel K, Andrykowski MA. Physical and mental health status and health behaviors of childhood cancer survivors: findings from the 2009 BRFSS survey. Pediatr Blood Cancer 2012;58:964–70.
51. Smith WA, Nolan VG, Robison LL, Hudson MM, Ness KK. Physical activity among cancer survivors and those with no history of cancer—a report from the National Health and Nutrition Examination Survey 2003–2006. Am J Transl Res 2011;3(4):342–50.
52. Badr H, Paxton RJ, Ater JL, Urbauer D, Demark-Wahnefried W. Health behaviors and weight status of childhood cancer survivors and their parents: similarities and opportunities for joint interventions. J Am Diet Assoc 2011;111:1917–23.
53. Finnegan L, Wilkie DJ, Wilbur J, Campbell RT, Zong S, Katula S. Correlates of physical activity in young adult survivors of childhood cancers. Oncol Nurs Forum 2007;34:E60–9.
54. Keats MR, Courneya KS, Danielsen S, Whitsett SF. Leisure-time physical activity and psychosocial well-being in adolescents after cancer diagnosis. J Pediatr Oncol Nurs 1999;16(4):180–8.
55. Keats MR, Culos-Reed SN, Courneya KS, McBride M. An examination of physical activity behaviors in a sample of adolescent cancer survivors. J Pediatr Oncol Nurs 2006;23(3):135–42.
56. Mayer EI, Reuter M, Dopfer RE, Ranke MB. Energy expenditure, energy intake and prevalence of obesity after therapy for acute lymphoblastic leukemia during childhood. Horm Res 2000;53:193–9.
57. Mulhern RK, Tyc VL, Phipps S, Crom D, Barclay D, Greenwald C, Hudson M, Thompson EI. Health-related behaviors of survivors of childhood cancer. Med Pediatr Oncol 1995;25:159–65.
58. Oeffinger KC, Buchanan GR, Eshelman DA, Denke MA, Andrews TC, Germak JA, Tomlinson GE, Snell LE, Foster BM. Cardiovascular risk factors in young adult survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2001;23:424–30.
59. Paxton RJ, Jones LW, Rosoff PM, Bonner M, Ater JL, Demark-Wahnefried W. Associations between leisure-time physical activity and health-related quality of life among adolescent and adult survivors of childhood cancers. Psychooncology 2010;19:997–1003.
60. Polgreen LE, Petryk A, Dietz AC, Sinaiko AR, Leisenring W, Goodman P, Steffen LM, Perkins JL, Dengel DR, Baker KS, et al. Modifiable risk factors associated with bone deficits in childhood cancer survivors. BMC Pediatr 2012;12:40.
61. Tercyak KP, Donze JR, Prahlad S, Mosher RB, Shad AT. Multiple behavioral risk factors among adolescent survivors of childhood cancer in the Survivor Health and Resilience Education (SHARE) program. Pediatr Blood Cancer 2006;47:825–30.
62. Tillmann V, Darlington AS, Eiser C, Bishop NJ, Davies HA. Male sex and low physical activity are associated with reduced spine bone mineral density in survivors of childhood acute lymphoblastic leukemia. J Bone Miner Res 2002;17(6):1073–80.
63. Tyc VL, Hadley W, Crockett G. Prediction of health behaviors in pediatric cancer survivors. Med Pediatr Oncol 2001;37:42–6.
64. Elkin TD, Tyc VL, Hudson M, Crom D. Participation in sports by long-term survivors of childhood cancer. J Psychosoc Oncol 1998;16:63–73.
65. Caspersen CJ, Pereira MA, Curran KM. Changes in physical activity patterns in the United States, by sex and cross-sectional age. Med Sci Sports Exerc 2000;32:1601–9.
66. Song M, Carroll DD, Fulton JE. Meeting the 2008 physical activity guidelines for Americans among U.S. youth. Am J Prev Med 2013;44:216–22.
67. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008;40:181–8.
68. Hocking MC, Schwartz LA, Hobbie WL, Derosa BW, Ittenbach RF, Mao JJ, Ginsberg JP, Kazak AE. Prospectively examining physical activity in young adult survivors of childhood cancer and healthy controls. Pediatr Blood Cancer 2013;60:309–15.
69. Rueegg CS, von der Weid NX, Rebholz CE, Michel G, Zwahlen M, Grotzer M, Kuehni CE; Swiss Paediatric Oncology Group. Daily physical activities and sports in adult survivors of childhood cancer and healthy controls: a population-based questionnaire survey. PLoS ONE 2012;7:e34930.
70. Zhang FF, Roberts SB, Parsons SK, Must A, Kelly MJ, Wong WW, Saltzman E. Low levels of energy expenditure in childhood cancer survivors: implications for obesity prevention. J Pediatr Hematol Oncol 2014; Nov 6 (Epub ahead of print).
71. Reilly JJ, Ventham JC, Ralston JM, Donaldson M, Gibson B. Reduced energy expenditure in preobese children treated for acute lymphoblastic leukemia. Pediatr Res 1998;44:557–62.
72. Roberts SB. Use of the doubly labeled water method for measurement of energy expenditure, total body water, water intake, and metabolizable energy intake in humans and small animals. Can J Physiol Pharmacol 1989;67:1190–8.
73. Schoeller DA. Measurement of energy expenditure in free-living humans by using doubly labeled water. J Nutr 1988;118:1278–89.
74. Chow EJ, Pihoker C, Hunt K, Wilkinson K, Friedman DL. Obesity and hypertension among children after treatment for acute lymphoblastic leukemia. Cancer 2007;110:2313–20.
75. Jansen H, Postma A, Stolk RP, Kamps WA. Acute lymphoblastic leukemia and obesity: increased energy intake or decreased physical activity? Support Care Cancer 2009;17:103–6.
76. Reilly JJ, Brougham M, Montgomery C, Richardson F, Kelly A, Gibson BE. Effect of glucocorticoid therapy on energy intake in children treated for acute lymphoblastic leukemia. J Clin Endocrinol Metab 2001; 86:3742–5.
77. la Fleur SE, Akana SF, Manalo SL, Dallman MF. Interaction between corticosterone and insulin in obesity: regulation of lard intake and fat stores. Endocrinology 2004;145:2174–85.
78. Stern M, Lamana L, Russell C, Edwin L, Thompson A, Trapp S, Bitsko M, Mazzeo S. Adaptation of an obesity intervention program for pediatric cancer survivors (NOURISH-T). Clinical Practice in Pediatric Psychology 2013;1:264–75.
79. Arroyave WD, Clipp EC, Miller PE, Jones LW, Ward DS, Bonner MJ, Rosoff PM, Snyder DC, Demark-Wahnefried W. Childhood cancer survivors' perceived barriers to improving exercise and dietary behaviors. Oncol Nurs Forum 2008;35:121–30.
80. Samaan MC, Thabane L, Burrow S, Dillenburg RF, Scheinemann K. Canadian Study of Determinants of Endometabolic Health in Children (CanDECIDE study): a cohort study protocol examining the mechanisms of obesity in survivors of childhood brain tumours. BMJ Open 2013;3(6). pii: e002869.
81. Sklar CA, Mertens AC, Walter A, Mitchell D, Nesbit ME, O'Leary M, Hutchinson R, Meadows AT, Robison LL. Changes in body mass index and prevalence of overweight in survivors of childhood acute lymphoblastic leukemia: role of cranial irradiation. Med Pediatr Oncol 2000;35:91–5.
82. von Deneen KM, Liu Y. Obesity as an addiction: why do the obese eat more? Maturitas 2011;68:342–5.
83. Cohen H, Bielorai B, Harats D, Toren A, Pinhas-Hamiel O. Conservative treatment of L-asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2010;54: 703–6.
84. Halton JM, Nazir DJ, McQueen MJ, Barr RD. Blood lipid profiles in children with acute lymphoblastic leukemia. Cancer 1998;83:379–84.
85. Parsons SK, Skapek SX, Neufeld EJ, Kuhlman C, Young ML, Donnelly M, Brunzell JD, Otvos JD, Sallan SE, Rifai N. Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. Blood 1997;89:1886–95.
86. Mohn A, Di Marzio A, Capanna R, Fioritoni G, Chiarelli F. Persistence of impaired pancreatic beta-cell function in children treated for acute lymphoblastic leukaemia. Lancet 2004;363:127–8.
87. Patrick H, Nicklas TA. A review of family and social determinants of children's eating patterns and diet quality. J Am Coll Nutr 2005;24:83–92.

88. Mozaffarian D, Afshin A, Benowitz NL, Bittner V, Stephen R, Daniels SR, Franch HA, Jacobs DR, Kraus WE, Kris-Etherton PM, et al. Population approaches to reduce cardiometabolic risk factors by improving diet, physical activity, and smoking habits: a scientific statement from the American Heart Association. Circulation. 2012;126:1514–63
89. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, Bandera EV, Hamilton KK, Grant B, McCullough M, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:243–74.
90. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity and the prevention of cancer: a global perspective. Washington (DC): World Cancer Research Fund/American Institute for Cancer Research; 2007.
91. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers [cited 2014 Oct 1]. Available from: http://www.survivorshipguidelines.org/.
92. National Cancer Policy Forum; Institute of Medicine. Identifying and addressing the needs of adolescents and young adults with cancer: workshop summary. Washington (DC): The National Academies Press; 2014. Washington (DC).
93. Epstein LH, Valoski A, Wing RR, McCurley J. Ten-year follow-up of behavioral, family-based treatment for obese children. JAMA 1990;264:2519–23.
94. Golan M, Crow S. Targeting parents exclusively in the treatment of childhood obesity: long-term results. Obes Res 2004;12:357–61.
95. Golan M, Kaufman V, Shahar DR. Childhood obesity treatment: targeting parents exclusively v. parents and children. Br J Nutr 2006;95:1008–15.