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Dietary Intake and Diet Quality of Hematopoietic Stem Cell Transplantation Survivors

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Hematopoietic stem cell transplantation (HCT) survivors are burdened by a high prevalence and early onset of chronic diseases. Healthy dietary patterns have been associated with lower risks of chronic health conditions in the general population. HCT survivors are susceptible to multiple complications that may result in chronic illness. Unfortunately, no study to date has comprehensively documented the adherence of HCT survivors to the Dietary Guidelines for Americans (DGA), which are designed specifically to provide guidance for making healthy food choices. The primary aim of this study was to evaluate diet quality and nutrient intake adequacy of HCT survivors. A secondary aim was to assess these survivors' willingness to take part in a future dietary intervention. The dietary intake of adults who had undergone autologous or allogeneic HCT for a hematologic disease and were at least 1 year post-transplantation was assessed using the Block 2014 food frequency questionnaire, and diet quality was estimated using the Healthy Eating Index 2015. Nutrient intake adequacies of the group were estimated by the estimated average requirement cutpoint method. Survivors' (n = 90) HEI-2015 scores averaged 61.6 ± 1.1. Adherence to a good-quality diet was reported by only 10% of survivors. Intakes of vitamins A, C, and D, as well as magnesium and calcium, suggested inadequacy. Fiber intake at 8.9 g per 1000 kcal/day fell below the recommended adequate intake. "Change in taste" was associated with lower quality of diet (P = .02). HCT survivors within 2 years post-transplantation were more receptive than survivors beyond 2 years to participating in a dietary intervention (95% versus 65%; P = .0013). Adult HCT survivors reported less-than-optimal adherence to the 2015-2020 DGA and had numerous shortfall nutrient intakes; however, their willingness to participate in a dietary intervention was relatively high. These findings reinforce the need to incorporate nutrition into HCT survivor care.

INTRODUCTION

Hematopoietic stem cell transplantation (HCT) is potentially a curative treatment option for variety of hematologic diseases. Advances in the field of HCT over the past decade due to safer conditioning regimens, better post-transplantation supportive care, and alternative graft sources have markedly increased the number of transplantations performed, leading to increased numbers of long-term survivors. There were 108,900 HCT survivors in United States in 2009 (67,000 autologous (auto-) HCT survivors and 41,900 allogeneic (allo-) HCT survivors) [1]. The number of HCT survivors is estimated to increase to 242,000 by the year 2020 and to 502,000 by 2030. This success has also brought the recognition of long-term health impacts of HCT. The mortality rate among long-term survivors of allo-HCT is 4- to 9-fold higher than age-adjusted general population for at least 30 years after transplantation [2,3]. Late complications leading to substantial morbidity and mortality of HCT survivors include, but are not limited to, chronic graft-versus-host disease, cardiopulmonary complications, musculoskeletal disorders, endocrinopathies, and subsequent malignancies. Thus, substantial efforts are underway to develop practical approaches to prevent, screen for, and manage these late complications in the hope of reducing morbidity and mortality associated with HCT.

Higher rates of comorbidity among HCT survivors support the need for lifestyle interventions that target this vulnerable population. Nutrition is one of the modifiable factors that may

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prevent the long-term complications and delay the onset of chronic diseases in HCT survivors [4-6]. Allo-HCT recipients are at high risk for malnutrition immediately after transplantation due to conditioning regimen-related gastrointestinal complications, including mucositis, nausea, vomiting, and diarrhea, leading to an inability to maintain adequate oral intake and malabsorption [7,8]. Although several studies have documented HCT survivors' poor nutritional status in the acute post-transplantation phase, no study to date has comprehensively documented their long-term intake of key nutrients and adherence to the Dietary Guidelines for Americans (DGA). The aims of this study were to evaluate diet quality and the extent to which HCT survivors adhere to the DGA and to determine the adequacy of nutrient intake. A secondary aim was to assess their willingness to take part in a future nutritional program or dietary intervention.

METHODS

Study Population

Participants were identified from the University of Florida's Bone Marrow Transplant Program. The study population consisted of adults (age ≥18 years) who had undergone auto-HCT or allo-HCT for a hematologic disease and had survived at least 1 year post-transplantation. Individuals with disease relapse or active late acute or chronic graft-versus-host disease on immunosuppression were excluded. The study was conducted in accordance with the Declaration of Helsinki. All procedures involving human subjects were approved by the University of Florida's Institutional Review Board. Written informed consent was obtained from each subject.

Dietary Assessment

In this noninterventional cross-sectional study, dietary intake was assessed using the Block 2014 food frequency questionnaire (FFQ), which combines a full-length FFQ with a brief physical activity screening tool [9]. The food and beverage list included 127 items and reflects intake over the past 12 months, plus additional questions to adjust for fat, protein, carbohydrate, sugar, and whole-grain content. National Health and Nutrition Examination Survey dietary recall data were used to develop the food list in the Block 2014 FFQ. The nutrient and food group analysis database were developed from the US Department of Agriculture's Food and Nutrient Database for Dietary Studies 5.0, the Food Pyramid Equivalents Database, and the Nutrient Database for Standard Reference. The Block 2014 FFQ evaluates the frequency of consumption in 8 categories: never/hardly ever, once per month, 2 to 3 times per month, once per week, 2 to 3 times per week, 4 to 6 times per week, once per day, and ≥2 times per day. A portion size pictures document ed as a visual aid to enhance the accuracy of quantifications. Block 2014 FFQ was previously validated with repeated 24-hour dietary recalls and revealed a reasonable correlation (r =.4 to .7). Trained staff provided the study participants with detailed instructions on how to complete the self-administered Block 2014 FFQ and checked the completeness and accuracy of responses.

Diet Quality

The Healthy Eating Index (HEI) 2015 [10] total score and component scores and mean nutrient intake values were computed from the Block 2014 FFQ. The HEI is a measure of diet quality used to assess compliance with the US DGA. The HEI is composed of 9 adequacy components and 4 moderation components. Adequacy components represents the food group, subgroups, and dietary elements that are encouraged. Moderation components represent the food groups, subgroups, and dietary elements of which limited consumption is recommended [10,11]. HEI scores range from 0 to 100, with a higher score indicating a healthier overall diet. A HEI score <50 implies a poor diet quality, 51 to 80 indicates a diet that needs improvement, and >81 indicates good diet quality.

Self-Awareness of Dietary Quality

In this study, the term "dietary awareness" is meant to capture the participants' self-perception of diet quality. Level of awareness was assessed by using the question "In general, how healthy is your overall diet?", a valid, single-item measure of diet quality [12]. The answers were classified as "excellent," "very good," "good," "fair" or "poor."

Receptivity to Participate in a Diet Intervention

Receptivity to participate in a dietary intervention to stay healthy was assessed by the question, "How willing would you be to take part in a healthy nutrition program or diet intervention?" Response categories included "not at all," "somewhat," and "definitely." Those responding "somewhat" or "definitely" were asked additional questions to assess program preferences, including in-clinic nutrition consultation or a telephone, mail, or computer-based dietary guide.

Statistical Analysis

Demographic data, lifestyle and transplantation characteristics, and self-reported gastrointestinal symptoms were collected during the clinic visit using a questionnaire (Supplementary Materials). A linear model was used to assess whether diet quality was affected by HCT survivors' demographic characteristics, lifestyle factors, and transplantation characteristics listed in Supplementary Table S1. The chi-square test was used to test the association between the study participants' opinions about participating in a future dietary intervention (definitely, somewhat, or not at all) and their demographic characteristics, lifestyle factors, and transplantation characteristics. The chi-square test was also used to test the association between diet quality awareness and assessed quality of diet, and Fisher's exact test was used when sample sizes were small. A P value <.05 was considered statistically significant. Mean nutrient intakes of the group were compared with the estimated average requirements (EARs) of the Dietary Reference Intakes [13], which is the median requirement for each nutrient. The percentage of HCT participants falling below the EAR for each nutrient was calculated as the prevalence of inadequate intake.

RESULTS

Between December 2017 and September 2018, 124 survivors were eligible for the study. Of these patients, 109 were contacted and 107 consented to participate. Two participants died before completing the study, and 3 did not follow through with participation. Data were collected for 102 participants, of whom 90 completed the dietary intake assessment and were included in the present analysis. Participant and transplantation characteristics are compiled in Table 1. The mean age of study participants at enrollment was 59 ± 11 years, and the mean interval from HCT was 5.2 ± 4.1 years. The majority of participants were male (55.6%), white (71.1 %), and married (78.9%). Approximately one-half of participants had some college education (51.7%), and the majority had an annual household income exceeding $50,000. The majority of participants were overweight (34.4%) or obese (36.7%). Approximately 26% of the participants were former smokers, and only 3.8% were active smokers. The majority of the participating HCT survivors had undergone auto-HCT (57%) and received myeloablative conditioning (67%).

Diet Quality in HCT Survivors

The HEI-2015 and component scores are presented in Table 2. The mean HEI-2015 score was 61.6 ± 1.1 out of a maximum score of 100. All component scores were below optimum. HEI-2015 scores were used to assess diet quality by categorizing HCT survivors into 3 categories: poor diet quality, needs improvement. and good diet quality. Of the survivors, 74 required some improvement in their diet quality, and 7 had a poor-quality diet. A good-quality diet was observed in only 10% of survivors (n = 9). In the final multivariable model, self-reported change in taste was the sole factor associated with lower quality of diet in HCT survivors (P= .02) (Supplementary Table S1).

Nutrient Intake

HCT survivors' nutrient intake from food are summarized in Table 3. Intake of vitamins A, C, and D and folate, as well as of magnesium and calcium, suggested a high risk of inadequacy in this population, with >50% of the group falling below the respective EAR recommendation. Fiber intake at 8.9 g per 1000 kcal/day was significantly below the adequate intake of 14 g per 1000 kcal/day as was potassium intake. The mean sodium intake of 2834 ± 1345 mg/day exceeded the tolerable upper limit of 2300 mg/day.

Table 1
Participant Demographic Characteristics and HCT History

Characteristic	Value
Sex (N = 90), n (%)	
Males	50 (55.6)
Females	40 (44.4)
Current age, yr, mean ± SD (range)	59 ± 11 (23-77)
Age at transplant, yr, mean ± SD (range)	54 ± 12 (20-75)
Race (N = 90), n (%)	
White	64 (71.1)
African American	20 (22.2)
Other	6 (6.7)
Body mass index, kg/m^2 (N = 90), n (%)	
Underweight (<18.5)	1 (1.1)
Normal weight (18.5-24.9)	25 (27.8)
Overweight (25-29.9)	31 (34.4)
Obese (≥30)	33 (36.7)
Education (N = 89), n (%)	
≤High school graduate	26 (29.2)
Some college or college graduate	46 (51.7)
Post graduate degree	17 (19.1)
Employment Status (N = 90), % (n)	
Employed	30 (33.3)
Unemployed/retired	60 (66.7)
Household income (N = 84), n (%)	
<$25,000	14 (16.7)
$25,000-$50,000	21 (25.0)
>$50,000	49 (58.3)
Marital status (N = 90), n (%)	
Married	73 (78.9)
Divorced	11 (12.2)
Single (never married)	3 (3.3)
Widowed	3 (3.3)
Smoking status (N = 89), n (%)	
Current smoker	3 (3.4)
Former smoker	23 (25.8)
Nonsmoker	63 (70.9)
Type of transplantation (N = 90), n (%)	
Autologous	51 (56.7)
Allogeneic	39 (43.3)
Primary disease (N = 90), n (%)	
Myeloma	44 (48.9)
Acute myelogenous leukemia/myelodysplastic syndrome	11 (12.2)
Lymphoma	12 (13.3)
Acute lymphoblastic leukemia	8 (8.9)
Other*	15 (16.7)
Conditioning regimen (N = 90), n (%)	
Myeloablative	60 (66.7)
Nonmyeloablative	30 (33.3)
Interval since HCT, yr (N = 90), mean ± SD	5.2 ± 4.1
Symptoms, yes/no, (N = 90)	
Nausea/vomiting	11/79
Abdominal discomfort	20/70
Change in taste	26/64
Difficulty swallowing	9/81

* Myeloproliferative diseases, Aplastic anemia.

Self-Awareness of Dietary Quality

Among the 88 participants who responded to the diet quality awareness question, 44 (50%) reported good, 25 (28%) reported excellent/very good, and 16 (18%) reported fair diet quality. Only 3.4% (n = 3) of the participants reported consuming a poor-quality diet. Figure 1 displays the association between self-perception of diet quality, as defined in 4 categories (excellent/very good, good, fair, and poor) and mean HEI-2015 scores. Survivors' dietary awareness was positively associated with actual diet quality as assessed by HEI-2015 (P = .0007).

Receptivity to Participate in a Dietary Intervention

Among the 90 participants, only 30 (33%) reported that they had received dietary guidance from their transplantation physicians. More than two-thirds of the participants were "definitely" or "somewhat" interested in participating in nutrition program or dietary intervention (n = 64; 72.7%). Of the 88 respondents, 27 (30.6%) considered it appropriate to be contacted by email, 16 (18.1%) by mail, 13 (14.7%) by an in-person visit, and 5 (5.6 %) by telephone regarding a nutrition program or dietary intervention. Based on the multivariate analysis, time since HCT significantly influenced willingness to participate in a dietary intervention. More specifically, HCT survivors within 2 years of transplantation were more likely to be receptive to participating in a nutrition program or diet intervention compared with survivors beyond 2 years after transplantation (95% versus 65%; P= .0013). Other transplantation and patient characteristics, including educational level, annual family income, employment status, marital status, and household status, were not associated with willingness to participate in a dietary intervention.

DISCUSSION

Long-term HCT survivors are burdened by a high prevalence and early onset of chronic diseases. Based on a previous study evaluating the chronic disease burden in 1022 HCT recipients [14], compared with their siblings, HCT survivors were twice as likely to develop a chronic health disease of any severity, with a cumulative incidence of 59% at 10 years after transplantation. Previous studies also have demonstrated that HCT survivors continue to experience premature death long after HCT due to chronic health conditions as a consequence of HCT [15,16]. The known associations between healthy dietary patterns and a reduced risk of chronic health conditions in the general population, including metabolic syndrome [17,18], cardiovascular disease [19], hyperlipidemia, and diabetes [20], reinforces the importance of evaluating nutrition and diet quality in the care of HCT survivors.

The limited number of studies characterizing diet and its influence on post-HCT complications published to date have focused mainly on early peritransplantation nutrition [21-24]. To our knowledge, the present study provides the first detailed evaluation of nutrient intake and diet quality in a group of adult long-term HCT survivors. In this cross-sectional study, we identified evidence of less-than-optimal adherence of HCT survivors to the 2015 DGA intended to promote health. Compared with a representative sample of Americans, participants in the present study had a similar mean HEI-2015 score (62 versus 58) [10], but the data suggest that they differ in individual component scores. They scored lower for the moderation components of sodium and saturated fat as well as in adequacy scores of total protein and seafood and plant proteins. In contrast, the HCT survivors scored somewhat higher for the fruit- and vegetable-related and whole-grain components. However, improvements in each diet quality component score are needed. More specifically, HCT survivors would benefit from increased intake of -plant-based foods, including fruits,

Table 2
HEI-2015 and Component Scores of HCT Survivors and the US Population

Component	Maximum Score	Standard for Maximum Score	FFQ Respondents (n = 90) HEI-2015 Score (SE)	General Population HEI-2015 Score [10]
Adequacy score				
Total fruits	5	≥.8 c equivalents	3.1 (.2)	2.4
Whole fruits	5	≥.4 c equivalents	3.9 (.1)	3.5
Total vegetables	5	≥1.1 c equivalents	3.8 (.1)	3.3
Greens and beans	5	≥.2 c equivalents	3.6 (.2)	3.2
Whole grains	10	≥1.5-oz equivalents	4.0 (.3)	2.5
Dairy	10	≥1.3 c equivalents	5.7 (.2)	5.9
Total protein foods	5	≥2.5-oz equivalents	4.5 (.1)	5.0
Seafood and plant proteins	5	≥.8-oz equivalents	3.9 (.1)	5.0
Fatty acids	10	(PUFAs + MUFAs)/ SFAs ≥2.5	5.4 (.3)	4.6
Moderation score				
Refined grains	10	≤1.8-oz equivalents	8.1 (.3)	6.3
Sodium	10	≤1.1 g	3.3 (.3)	3.9
Added sugars	10	≤6.5% of energy	7.2 (.3)	6.4
Saturated fats	10	≤8% of energy	5.2 (.3)	6.0
Total HEI score	100		61.6 (1.1)	58.0

PUFA indicates polyunsaturated fat; MUFA, monounsaturated fat; SFA, saturated fat.

vegetables, and beans; substitution of refined-grain foods for whole grains; and decreased added sugar and saturated fat intake. In addition to diet quality, nutrient intakes suggest that some of the HCT survivors are consuming inadequate amounts of vitamin D and calcium among other marginal nutrients. Dietary change, such as increased intake of dairy foods, may improve both diet quality and intake of these nutrients. In contrast to previous studies [25-27], we did not observe differences in diet quality according to race, age, sex, or socioeconomic status of HCT survivors. This may be related to the single-center nature of our study with a sample population skewed toward older, white, and socioeconomically advantaged individuals.

Table 3
Nutrient Intake of HCT Survivors

Nutrient	Intake (N = 90)	Recommendation	Proportion at Risk for Inadequacy, %
Energy, kcal	1630 ± 770		
Protein, g	61 ± 30		
% of total energy	15	10-35*	
Carbohydrate, g	197 ± 109	100†	14.4
% of total energy	48	45-65*	
Fiber, g/1000 kcal	8.9 ± 5.3	14‡	
Added sugar, g/d	54 ± 11		
% of total energy	13	<10	
Total fat	68 ± 64	27	
% of total energy	37	20-35*	
Saturated fat, g	25 ± 12		
% of total energy	11	<10%	
Vitamin A, μg/d	720 ± 447	500-625†	55.3
Vitamin C, mg/d	82 ± 73	60-75†	57.8
Vitamin D, μg/d	4.4 ± 3.4	10†	96.7
Thiamin, mg/d	1.7 ± .9	.9-1.0†	13.0
Vitamin B6, mg/d	1.6 ± .9	1.1-1.4†	41.1
Vitamin B12, μg/d	4.4 ± 2.5	2.0†	12.2
Folate, g/d	324 ± 167	320†	56.7
Calcium, mg/d	781 ± 430	800-1000†	76.7
Iron, mg/d	12 ± 6	6-8†	21.1
Magnesium, mg/d	253 ± 133	265-350†	63.3
Potassium, mg	2229 ± 1173	4700‡	
Phosphorus, mg	1093 ± 528	580†	11.1
Sodium, mg	2834 ± 1345	1500‡/2300§	

* Acceptable macronutrient distribution range.
† Estimated average requirement.
‡ Adequate intake.
§ Tolerable upper limit.

In this study, altered taste perception was the sole variable associated with diet quality. More specifically, HCT survivors who reported persistent taste alteration had significantly lower diet quality. Altered taste perception has been shown to play an important role in food selection and metabolism and, consequently, body weight [28,29]. Although significant alterations in the sense of taste during treatment with chemotherapy or radiation have been well documented, long-term taste dysfunction in HCT survivors has not been studied extensively. In a retrospective study of 15 allo-HCT survivors, late and selective taste disorders, including a significant hypogeusia for salt and sour, were observed compared with healthy individuals [30]. In a more recent study evaluating taste alterations in survivors of childhood cancer, 27.5% of survivors suffered from taste dysfunction, a rate 3 times higher than that in the non-cancer population [31]. Similarly, our study identified persistent taste dysfunction in nearly one-third of adult long-term HCT survivors, approximately twice as high as the rate of self-reported taste alteration in the US general population over age 40 (28.8% versus 17.5%) [32]. Further work is needed to better understand the prevalence of taste alteration and assess whether taste dysfunction plays a role in the dietary habits of long-term transplantation survivors.

Interestingly, self-rated diet quality was associated with an objective measure of dietary intake using FFQ in this population. Current measurements of diet quality rely on lengthy questionnaires, which can be time-consuming and burdensome for patients and difficult to administer in the clinic setting to large numbers of patients. Therefore, a single-item measure of self-rated diet quality may be a simple and practical approach to identify patients with poor diet quality who need dietary improvement and thus may benefit from nutritional programs and/or dietary interventions.

The majority of the study participants (70%) reported a willingness to receive nutritional advice and participate in a

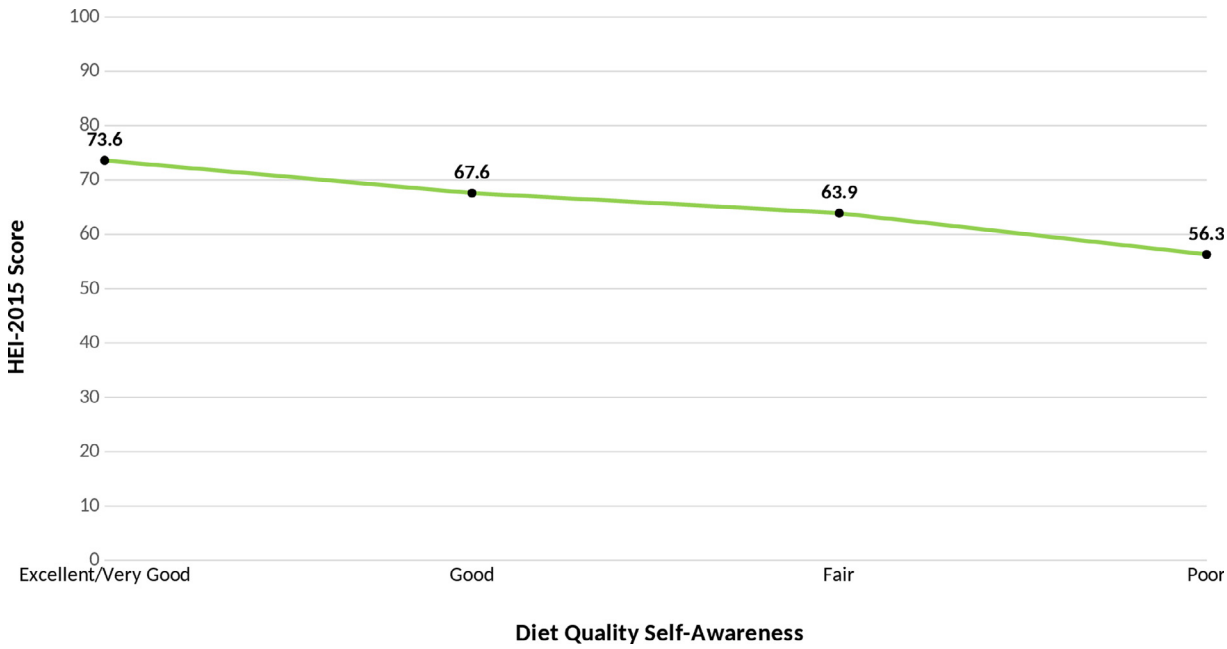

Figure 1. Association between diet quality self-awareness and HEI-2015 score ($P = .0007$).

dietary intervention. This finding is similar to previous studies indicating cancer survivors' high levels of interest in multiple behavior interventions [33,34]. Despite the high level of interest, only 30% of HCT survivors acknowledged receiving nutrition guidance from their transplantation physician. Given the importance of the physician's role in reinforcing health-promoting behaviors [35], it is imperative that transplantation physicians take a more active role in health promotion and be able to provide at least basic evidence–based nutritional advice. Future studies to evaluate the challenges and barriers for transplantation physicians to provide nutrition recommendations to their patients and strategies for improving physician engagement with nutrition interventions and referral to registered dietitian nutritionist are needed.

Time since transplantation was also identified as a relevant factor in long-term survivors' willingness to participate in a dietary intervention trial. Based on a previous study of 10,632 HCT survivors, the risk of disease relapse decreases significantly, and the prospect for long-term survival is excellent for 2-year survivors of HCT [3]. Reduced interest in nutrition guidance or dietary intervention in HCT survivors beyond 2 years after transplantation may be explained by long-term survivors' perception of diminished benefit from lifestyle changes as their illness becomes less salient over time or a lack of knowledge regarding long-term complications of cancer and cancer therapy beyond disease relapse.

This study has several limitations that need to be considered, including a relatively small sample size, which limited detection of small differences in diet quality based on patient or treatment/transplantation characteristics, and lack of a healthy control group. In addition, participants were recruited from a long-term follow up clinic, which might have led to the selection of individuals more likely to engage in health promotion behaviors. Furthermore, the current findings might not apply to HCT survivors with chronic graft-versus-host disease, and thus this population should be studied. Another limitation is the inherent recall bias of the FFQ. More specifically, the accuracy of dietary questionnaires depends on the subject's ability to describe the type and quantity of food consumed. Owing to the cross-sectional nature of this study, associations between diet and clinical endpoints, such as occurrence of chronic health conditions, were not evaluated.

Despite its limitations, this study provides valuable insight into the nutritional intake of adult HCT survivors. Our cohort of adult HCT survivors reported less-than-optimal adherence to the 2015 DGA and numerous shortfall nutrient intakes. However, the survivors' willingness to participate in a nutrition program or dietary intervention was relatively high. These findings reinforce the need to incorporate nutrition assessment and awareness into HCT survivor care. Future studies are needed to better understand the effect of food intake and dietary patterns on clinical outcomes among long-term HCT survivors, investigate barriers to a healthy diet, and identify the optimal nutritional support in this population.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2020.02.017.

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