ARTICLE

Performance Limitations and Participation Restrictions Among Childhood Cancer Survivors Treated With Hematopoietic Stem Cell Transplantation

The Bone Marrow Transplant Survivor Study

Kirsten K. Ness, PhD; Smita Bhatia, MD, MPH; K. Scott Baker, MD, MS; Liton Francisco, BA; Andrea Carter, BA; Stephen J. Forman, MD; Leslie L. Robison, PhD; Joseph Rosenthal, MD; James G. Gurney, PhD

Background: Hematopoietic stem cell transplantation (HCT) may result in important disease- and treatment-related late effects. This study estimated physical, emotional, and educational limitations (performance limitations) and restrictions in the ability to perform personal care or routine daily activities (physical participation restrictions) and restrictions in the ability to participate in social roles (social participation restrictions) in a cohort of cancer survivors treated with HCT during childhood.

Methods: Study participants included 235 persons who had a malignancy or hematologic disorder, were treated with HCT before the age of 21 years, and survived at least 2 years after transplantation. A comparison group was recruited and frequency matched for age, sex, and ethnicity. Medical data were abstracted, and patients or parents (if <18 years at survey completion) completed a mailed 24-page questionnaire.

Results: Adult survivors of childhood cancer were more likely than the comparison group to report limitations in physical (prevalence odds ratio [OR], 2.2; 95% confidence interval [CI], 1.3-3.7) and emotional domains (OR, 2.9; 95% CI, 1.4-5.8) and to report physical participation restrictions (OR, 3.9; 95% CI, 1.9-8.2). Adult survivors were also less likely than the comparison group to be married (OR, 0.4; 95% CI, 0.2-0.6). Child survivors were more likely than similarly aged children to have participated in special education (OR, 3.0; 95% CI, 1.5-6.0), to report physical participation restrictions (OR, 10.8; 95% CI, 2.2-53.9), and to have behaviors that indicated impaired social competence (OR, 2.0; 95% CI, 0.9-4.2).

Conclusion: This study demonstrated that persons treated with HCT as children were at increased risk for performance limitations that restricted participation in routine daily activities and interpersonal relationships.

Arch Pediatr Adolesc Med. 2005;159:706-713

HEMATOPOIETIC STEM CELL transplantation (HCT) is used to treat a variety of malignant and nonmalignant disorders in children and adults.[1] Approximately 6000 HCTs are performed in the United States each year, with the number of recipients who are at least 5-year survivors estimated at 100 000.[2] Hematopoietic stem cell transplantation is associated with several disease-related and treatment-specific medical late effects[3-13] that have the potential to limit functional performance in physical, emotional, and educational domains. Over time, these limitations may adversely affect the individual's ability to participate fully in life's roles, such as engaging in daily activities or interacting socially.

Few studies of transplantation survivors have evaluated the prevalence of performance limitations across physical, emotional, and educational domains or the impact on the ability to participate physically and socially in life roles. Furthermore, few reports evaluate the association between performance limitations and participation restrictions in individuals who undergo transplantation during childhood.

The aims of this analysis were (1) to estimate the prevalence of performance limitations (physical, emotional, and educational) and physical and social participation restrictions in a cohort of patients who underwent transplantation before the age of 21 years and who survived at least 2 years after transplantation; (2) to compare performance limitations and participation restrictions in HCT survivors with those in

Author Affiliations: Department of Pediatrics, University of Minnesota, Minneapolis (Drs Ness, Baker, Robison, and Gurney); and City of Hope National Medical Center, Duarte, Calif (Drs Bhatia, Forman, and Rosenthal, Mr Francisco, and Ms Carter).

©2005 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/23/2013

a representative comparison group; and (3) to evaluate the extent to which performance limitations were associated with participation restrictions among HCT survivors.

METHODS

STUDY POPULATION

This analysis is part of the Bone Marrow Transplant Survivor Study (BMT-SS), a collaborative study between City of Hope Cancer Center and the University of Minnesota. Eligibility criteria for this analysis included (1) HCT for hematologic or nonhematologic malignancy; (2) date of transplantation between January 1, 1974, and December 31, 1998; and (3) survival of more than 2 years after HCT. This analysis was restricted to English-speaking survivors younger than 21 years at the time of their transplantation and alive at the time of the initial survey. The human subjects review committees at both institutions approved all study questionnaires and protocols. All participants provided informed consent.

A total of 528 eligible patients were identified. Of these, 136 (25.7%) were lost to follow-up, 131 (24.8%) declined participation, and 26 (4.9%) had yet to complete the study questionnaire. A total of 235 survivors or their proxies completed a study questionnaire, which represents 60.0% of those successfully contacted. The comparison group included siblings of another cohort of cancer survivors[14] who completed a questionnaire between 1996 and 2003 that contained identical study questions. Comparison group participants were frequency matched to cases at a ratio of 3:1 and randomly selected from 3845 eligible group members from within 6 age groups (<10 years, 11-14 years, 15-17 years, 18-29 years, 30-39 years, ≥40 years), 2 sex groups, and 2 race/ethnicity (white or other) categories.

DATA COLLECTION

Data collection was conducted by abstracting information from medical records and by having participants (aged ≥18 years at survey) or their parents (if participants were aged <18 years) complete the 24-page BMT-SS questionnaire about the presence and timing of medical conditions, the presence of performance limitations during a 2-year period before study participation, and the presence of current participation restrictions. This questionnaire has excellent (93%)[15] agreement with reported major medical conditions when compared with medical records information. Marital status, educational attainment, and a measure of emotional health, the Brief Symptom Inventory (BSI),[16] are part of the adult version of the BMT-SS. Participation in special education, social competence, and emotional health based on parental observation are included in the child version of the BMT-SS.

MEASURES

Participation Restrictions

Adults. The primary outcome measures for adult participants treated during childhood were physical participation restrictions and marital status. Participants were classified as having a physical participation restriction if they answered yes to either of 2 questions: "Because of any impairment or health problems, do you need the help of other persons with personal care needs, such as eating, bathing, dressing, or getting around your home?" or "Because of any impairment or health problems, do you need the help of other persons in handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?" Marital status was determined by participants' answers to the question, "Which of these possibilities best describes your current marital status?" A dichotomous value was assigned, in which 1 indicated married or living as married and 0 indicated unmarried.

Children. The primary outcome measures for younger participants were physical participation restrictions and social competence. Physical participation restrictions were classified as described for the adults. Social competence was scored by summing values from answers to 6 questions about current friendships and play behavior, adapted from the Child Behavior Checklist.[17] Scores ranged from 4 (a child who had no friends, participated in few social activities, did not get along with others, and did not play well alone) to 19 (a child who had many friends, participated in multiple social activities, got along well with others, and could self-entertain). After examining the distributions of social competence, this variable was dichotomized using a cutoff point at or below the comparison group 10th percentile to represent social participation restrictions.

Performance Limitations

The risk factors of interest were limitations in physical, emotional, and educational performance.

Adults. Physical performance was scored by summing the answers to 6 questions about performance of particular physical activities: "Over the past 2 years, how long (if at all) has your health limited you in each of the following activities? (1) vigorous activities like lifting heavy objects, running, or participating in strenuous sports, (2) moderate activities like moving a table, carrying groceries, or bowling, (3) walking uphill or climbing a few flights of stairs, (4) bending, lifting, or stooping, (5) walking one block, and (6) eating, dressing, bathing, or using the toilet." Scores of 1 to 3 were assigned to each question, with 1 indicating limited for more than 3 months; 2, limited for 3 months or less; and 3, not limited at all. This variable was also dichotomized using a cut point at or below the comparison group 10th percentile to indicate the presence of physical performance limitations. Emotional functioning was evaluated by scoring the BSI-18, an instrument designed to evaluate emotional health. Raw scores were converted to T scores based on population normative values provided in the scoring manual.[16] On the basis of previous work by Derogatis,[16] a T score of 63 or higher was used as the cutoff point for impaired emotional health. Educational attainment was classified according to participants' answers to the question, "What is the highest grade or level of schooling that you have completed?" Participants were classified into 3 categories: (1) did not complete high school, (2) high school graduate, and (3) college graduate.

Children. Physical performance among children was scored as described for adults. Children's emotional functioning was evaluated using a score based on 23 behavior questions answered by the child's parent. The construct validity of this portion of the questionnaire was evaluated in a larger population of childhood cancer survivors[14] using exploratory factor analysis, in which 5 factors were identified with maximum likelihood estimation. The correlations of the questions within and between each factor were identified to determine internal consistency. The mean values between participants and siblings were compared to evaluate discriminate validity (within-factor and between-factor correlations ranged from 0.75 to 0.89; survivors had higher scores than siblings, indicating greater problems with behaviors related to emotional health; $P<.001$). This variable was dichotomized using a cutoff point at or above the comparison group 90th percentile to indicate the presence of

©2005 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/23/2013

Table 1. Comparison of Study Participants and Eligible Nonparticipants

Characteristic	Participants, No. (%) (n = 235)	Nonparticipants, No. (%) (n = 267)	*P* Value
Sex			.02
Male	131 (55.7)	176 (65.9)	
Female	104 (44.3)	91 (34.1)	
Race			.06
White	199 (84.7)	205 (76.8)	
Hispanic	18 (7.7)	29 (10.9)	
Other	18 (7.7)	33 (12.3)	
Institution			.55
City of Hope	57 (24.3)	71 (26.6)	
University of Minnesota	178 (75.7)	196 (73.4)	
Age at transplantation, y			.22
0-4	61 (26.0)	57 (21.3)	
5-9	57 (24.3)	56 (21.0)	
10-20	117 (49.8)	154 (57.7)	
Primary diagnosis			.47
Leukemia	147 (62.6)	160 (59.9)	
Lymphoma	16 (6.8)	24 (9.0)	
Myelodysplastic syndrome	9 (3.8)	6 (2.2)	
Neuroblastoma	16 (6.8)	12 (4.5)	
Primitive neuroectodermal tumor	2 (0.9)	0	
Ewing sarcoma	5 (2.1)	2 (0.7)	
Aplastic anemia	31 (13.2)	55 (20.6)	
Fanconi anemia	7 (3.0)	5 (1.9)	
Other	2 (0.8)	3 (1.1)	
Transplantation type			.81
Allogeneic	177 (75.3)	210 (78.6)	
Autologous	58 (24.7)	57 (21.3)	
Stem cell source			.06
Marrow	210 (89.4)	249 (93.3)	
Peripheral stem cells	12 (5.1)	9 (3.4)	
Marrow and peripheral stem cells	3 (1.3)	6 (2.2)	
Cord blood	10 (4.3)	3 (1.1)	
Conditioning regimen			.19
TBI and chemotherapy	176 (74.9)	213 (79.8)	
Chemotherapy	59 (25.1)	54 (20.2)	
Chronic graft-vs-host disease			.27
Yes	46 (19.6)	63 (23.6)	
No	189 (80.4)	204 (78.4)	

Abbreviation: TBI, total body irradiation.

emotional performance limitations. Participation in special education was used as a crude measure of educational attainment among younger participants, recorded as a dichotomous variable based on the answer of the child's proxy to the question, "In elementary, junior high, or high school, was your child ever in a learning disabled or special education program because of low scores on tests, problems learning or concentrating, emotional-behavioral problems, or missed school?"

Transplantation-Related Variables and Medical Late Effects

Graft-vs-host Disease and Major Medical Conditions. The presence of chronic graft-vs-host disease (cGVHD) was determined by examining medical records. Consistent with the work of Hudson et al,[18] the following major medical late effects, reported by survivors since transplantation, were analyzed: complete deafness; kidney dialysis; congestive heart failure; a history of myocardial infarction; angioplasty; bypass surgery or stroke; liver cirrhosis; heart, lung, or kidney transplantation; amputation; joint replacement or a second cancer; and current use of seizure medications, medications for heart problems or high blood pressure, chemotherapy, immunosuppressants, or oxygen.[18]

Personal Characteristics. Personal characteristics included study participants' sex, race/ethnicity, age in years at survey completion, and age at transplantation, and time since transplantation.

STATISTICAL ANALYSES

All analyses were completed separately for participants younger than 18 years (children) at the time of the survey and those who were 18 years or older (adults). The analyses of educational attainment and marital status for adults were stratified into 2 groups to account for the possibility that 18- to 24-year-old survivors might still be completing formal education.

The HCT survivors were compared with the comparison group for the presence of a major medical condition, for each performance measure (physical, emotional, and educational), for physical participation restrictions and marital status (adults), or for physical and social participation restrictions (children) using multiple logistic regression. Restricting the analyses to the HCT survivor population only, logistic regression models were used to evaluate the association between the participants' personal characteristics, conditioning regimen, cGVHD, or a major medical condition among HCT survivors who reported physical, emotional, and educational performance limitations. Finally, to determine the relation between measures of performance and the outcome variables of physical participation restrictions, marital status (adults), and social participation restrictions (children), each measure of performance was evaluated in survivor-survivor comparisons using multiple logistic regression, adjusting for sex, ethnicity, time since transplantation in years, and age at survey completion.

RESULTS

PARTICIPANT CHARACTERISTICS

Participants were more likely than nonparticipants to be female (104 [44.3%] and 91 [34.1%], respectively) and white (199 [84.7%] vs 205 [76.8%]) but did not otherwise differ significantly from nonparticipants (**Table 1**). The mean age at survey completion was similar for the adult participants and the adult comparison group (mean ± SD, 26 ± 6 years). Among the children, both participants and members of the comparison group had mean ± SD ages of 13 ± 3 years. Mean age at transplantation was 10.7 ± 6.3 years, and mean survival time was 11.7 ± 5.7 years. The diagnosis and treatment characteristics of the study participants are given in **Table 2**.

SURVIVOR–COMPARISON GROUP ANALYSES

Major Medical Conditions

Adults. We documented cGVHD in 37 (23.4%) of participants. Fifteen (9.5%) of adults reported current use of cardiac medications, and 15 (9.5%) reported current use of immunosuppressants. The other most common medical conditions reported by adults were a history of second can-

©2005 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/23/2013

Table 2. Characteristics of the Study Participants and Comparison Groups

Characteristic	Adult Survivors, No. (%) (n = 157)	Adult Comparison Group, No. (%) (n = 471)	Child Survivors, No. (%) (n = 78)	Child Comparison Group, No. (%) (n = 234)
Sex				
Female	88 (56.0)	264 (56.0)	43 (55.1)	129 (55.1)
Male	69 (44.0)	207 (44.0)	35 (44.9)	105 (44.9)
Ethnicity				
White	127 (80.9)	381 (80.9)	72 (92.3)	216 (92.3)
Hispanic	17 (10.8)	51 (10.8)	1 (1.3)	2 (0.8)
Other	13 (8.3)	39 (8.3)	5 (6.4)	16 (6.8)
Age at survey, y				
<10	NA	NA	13 (16.7)	39 (16.7)
10-14	NA	NA	40 (51.3)	120 (51.3)
15-17	NA	NA	25 (32.0)	75 (32.0)
18-29	124 (79.0)	372 (79.0)	NA	NA
30-39	28 (17.8)	84 (17.8)	NA	NA
40-50	5 (3.2)	15 (3.2)	NA	NA
Time since transplantation, y				
2-5	24 (15.3)	NA	19 (24.3)	NA
6-10	41 (26.1)	NA	40 (51.3)	NA
≥11	92 (58.5)	NA	19 (24.3)	NA
Annual household income, $				
≤9999	8 (5.1)	0	1 (1.3)	0
10 000-19 999	17 (10.8)	40 (8.5)	1 (1.3)	11 (4.7)
20 000-39 999	38 (24.2)	117 (24.8)	12 (15.4)	52 (22.2)
40 000-59 999	29 (18.5)	98 (20.8)	11 (14.1)	68 (29.0)
≥60 000	46 (29.3)	138 (29.3)	18 (23.1)	83 (35.5)
Unknown	19 (12.1)	78 (16.6)	35 (44.9)	20 (8.5)

Abbreviation: NA, not applicable.

cer (14 [8.9%]) or stroke (9 [5.7%]). The HCT recipients were 10.3 times (95% confidence interval [CI], 6.1-17.4) more likely to report a major medical condition than were adults in the comparison group (data not shown).

Children. Nine (11.5%) of young survivors had documented cGVHD. Current use of cardiac medications was reported for 12 of children (15.4%), and current use of immunosuppressants was reported for 4 (5.1%). The other most common medical condition was congestive heart failure (4 children [5.1%]). Child survivors were 24.8 times (95% CI, 7.1-86.6) more likely to have a reported major medical condition than children in the comparison group (data not shown).

Performance Limitations and Participation Restrictions

Adults. Limitations in physical performance were reported by 28 (17.8%) of adult survivors compared with 42 adults (8.9%) in the comparison group (odds ratio [OR], 2.2; 95% CI, 1.3-3.7). Adult survivors were almost 3 times (OR, 2.9; 95% CI, 1.4-5.8) more likely to have a BSI score that indicated an emotional difficulty. No significant differences in educational attainment were observed. Adult survivors were 3.9 times (95% CI, 1.9-8.2) more likely to report physical participation restrictions than the comparison group (**Table 3**).

Children. Limitations in physical and emotional performance did not differ significantly between survivors and the comparison group, although HCT survivors were 3.0 times (95% CI, 1.5-6.0) more likely to have participated in special education. The HCT survivors were also more likely than the comparison group to report a physical participation restriction (9.0% vs 0.8%; OR, 10.8; 95% CI, 2.2-53.9) and were twice as likely to have reported behaviors that indicated social participation restrictions (Table 3).

SURVIVOR-SURVIVOR ANALYSIS

Performance Limitations

Adults. Adult survivors with physical performance limitations were more likely to have documented cGVHD (OR, 3.1; 95% CI, 1.3-7.5) or a reported major medical condition (OR, 3.4; 95% CI, 1.4-7.9) than those without physical performance limitations, after adjusting for age at interview and sex. Emotional performance limitations were not associated with any particular treatment variables or medical late effects. Adult survivors of races other than white were less likely than white survivors to graduate from high school (**Table 4**).

Children. After adjusting for sex, age at transplantation, cGVHD, and the presence of a major medical condition, the relative odds of a physical performance limitation were higher among the HCT survivors who had received total body irradiation (TBI) (OR, 15.9; 95% CI, 1.3-199.4) when compared with survivors who did not receive TBI. A strong association was also seen among

©2005 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/23/2013

Table 3. Performance Limitations and Participation Restrictions Among Survivors of Childhood HCT and Comparison Group

Limitation or Restriction	Survivors, No. (%) (n = 157)	Comparison Group, No. (%) (n = 471)	OR (95% CI)	*P* Value
		Performance Domains		
Physical performance limitation	28 (17.8)	42 (8.9)	2.2 (1.3-3.7)	.002
Emotional performance limitation	16 (10.2)	18 (3.8)	2.9 (1.4-5.8)	.003
Educational attainment				
18- to 24-year-olds				
<High school	10 (13.3)	22 (9.9)	1.6 (0.7-3.6)	.29
High school graduate	51 (68.0)	157 (70.7)	0.6 (0.3-1.5)	.29
College graduate	14 (18.7)	36 (16.2)	1.0 (0.4-2.1)	.93
Unknown	1 (1.3)	7 (3.2)	Not estimated	Not estimated
25- to 50-year-olds				
<High school	4 (4.9)	14 (5.6)	0.9 (0.9-1.1)	.73
High school graduate	40 (49.4)	100 (40.2)	1.2 (0.4-3.8)	.73
College graduate	37 (45.7)	119 (47.8)	0.8 (0.5-1.3)	.43
Unknown	0	16 (6.4)	Not estimated	Not estimated
		Participation Categories		
Physical participation restriction	17 (10.8)	14 (3.0)	3.9 (1.9-8.2)	.001
Marital status				
18- to 24-year-olds				
Currently married	8 (10.5)	36 (16.2)	0.4 (0.2-1.0)	.06
Not married	68 (89.5)	168 (75.7)	1.0	
Unknown	0	18 (8.1)	Not estimated	Not estimated
25- to 50-year-olds				
Currently married	34 (44.7)	150 (60.2)	0.4 (0.2-0.6)	<.001
Not married	47 (61.8)	84 (33.7)	1.0	
Unknown	0	15 (6.0)	Not estimated	Not estimated
		Performance Domains		
Physical performance limitation	12 (15.4)	20 (8.5)	1.9 (0.9-4.0)	.11
Emotional performance limitation	13 (16.7)	23 (9.8)	1.8 (0.8-3.7)	.13
Required special education	19 (24.4)	22 (9.4)	3.0 (1.5-6.0)	.002
		Participation Categories		
Physical participation restriction	7 (9.0)	2 (0.8)	10.8 (2.2-53.9)	.004
Social participation restriction	13 (16.7)	21 (9.0)	2.0 (0.9-4.2)	.07

Abbreviations: CI, confidence interval; HCT, hematopoietic stem cell transplantation; OR, odds ratio.

those who were more than 10 years past diagnosis (OR, 31.7; 95% CI, 1.2-812.1) relative to those who had survived 2 to 5 years. Emotional performance limitations and participation in special education were not associated with any particular personal characteristic, treatment regimen, or medical late effect in children (Table 4).

Participation Restrictions and Performance Limitations

Adults. The impact of the loss of performance on participation is given in **Table 5**. After adjusting for age at survey, time since transplantation, sex, and race/ethnicity, all domains of the performance limitations were associated with restricted abilities to perform personal care or to participate in routine activities among adult survivors of childhood HCT. Adult survivors with physical performance limitations were 22.1 times (95% CI, 6.3-77.9) more likely to need help with personal care or routine activities than those without physical performance limitations. Those with emotional performance limitations were 17.1-fold more likely (95% CI, 4.6-64.0) to report physical participation restrictions than those without, and participants who did not graduate from high school were 4.7 times (95% CI, 1.1-21.0) more likely than those who graduated from high school to report physical participation restrictions. Adult HCT survivors were 5 times less likely than those without physical performance limitations to be currently married (OR, 0.2; 95% CI, 0.1-0.9).

Children. Limitations in physical and emotional performance and the need for special education were associated with both physical and social participation restrictions in young HCT survivors (Table 5). Children with emotional performance limitations were 9.2 times (95% CI, 1.2-68.0) more likely than those without to have a physical participation restriction. These children were also far less able to participate socially, having 83.3 times (95% CI, 9.9-698.7) the risk of scoring within the lowest 10% of population norms when compared with children without an emotional performance limitation.

COMMENT

This study demonstrates that 10% of long-term HCT survivors who underwent transplantation during child-

©2005 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/23/2013

Table 4. Association Among Performance Limitations, Participant Characteristics, Chronic Graft-vs-host Disease, and Major Medical Condition Among Survivors of Childhood HCT

Variable	No. of Participants	Physical Performance Limitations			Emotional Performance Limitations			Did Not Graduate From High School		
		No. (%)	OR (95% CI)	*P* Value	No. (%)	OR (95% CI)	*P* Value	No. (%)	OR (95% CI)	*P* Value
Adults										
Sex										.91
Male	88	14 (15.9)	0.8 (0.4-1.7)	.58	6 (6.8)	0.4 (0.1-1.2)	.12	8 (9.1)	1.1 (0.3-3.2)	
Female	69	14 (20.3)	1.0		10 (14.5)	1.0		6 (8.7)	1.0	
Race/ethnicity										.004
White	127	20 (15.7)	0.5 (0.2-1.2)	.12	12 (9.4)	0.7 (0.2-2.2)	.53	7 (5.5)	0.2 (0.1-0.6)	
Other	30	8 (26.7)	1.0		4 (13.3)	1.0		7 (23.3)	1.0	
Age at transplantation, y										
0-4	14	1 (7.1)	0.7 (0.1-2.8)	.52	3 (21.4)	2.2 (0.5-9.2)	.26	1 (7.1)	1.0 (0.1-8.4)	.99
5-9	32	5 (15.6)	0.5 (0.2-1.9)	.46	1 (3.1)	0.3 (0.03-2.1)	.21	5 (15.6)	2.4 (0.7-8.3)	.16
10-20	111	22 (19.8)	1.0		12 (10.8)	1.0		8 (7.2)	1.0	
Time since transplantation, y										
2-5	92	6 (6.5)	1.5 (0.5-4.3)	.47	3 (3.3)	1.2 (0.3-4.6)	.82	2 (2.2)	1.1 (0.2-5.7)	.91
6-10	41	8 (19.5)	1.1 (0.4-2.7)	.89	3 (7.3)	0.6 (0.2-2.5)	.53	5 (12.2)	1.7 (0.5-5.8)	.37
11-27	24	14 (58.3)	1.0		10 (41.7)	1.0		7 (29.2)	1.0	
Conditioning regimen										.32
TBI and chemotherapy	128	24 (18.8)	1.7 (0.5-5.2)	.38	13 (10.2)	1.0 (0.3-3.9)	.97	10 (7.8)	0.5 (0.1-1.8)	
Chemotherapy only	29	4 (13.8)	1.0		3 (10.3)	1.0		4 (13.8)	1.0	
Chronic graft-vs-host disease										.61
Yes	37	13 (35.1)	3.1 (1.3-7.5)	.01	4 (10.8)	1.1 (0.3-3.6)	.89	4 (10.8)	1.4 (0.4-4.7)	
No	120	15 (12.5)	1.0		12 (10.0)	1.0		10 (8.3)	1.0	
Major medical condition										.53
Yes	56	18 (32.1)	3.4 (1.4-7.9)	.004	5 (8.9)	0.8 (0.3-2.4)	.69	6 (10.7)	1.4 (0.5-4.4)	
No	101	10 (9.9)	1.0		11 (10.9)	1.0		8 (7.9)	1.0	
Children										
Sex										.78
Male	43	5 (41.7)	0.5 (0.1-1.8)	.31	6 (46.2)	0.6 (0.2-2.1)	.5	11 (57.9)	1.2 (0.4-3.2)	
Female	35	7 (58.3)	1.0		7 (53.8)	1.0		8 (42.1)	1.0	
Race/ethnicity										.6
White	72	9 (75.0)	1.0		12 (92.3)	1.0 (0.1-9.3)	>.99	17 (89.5)	0.6 (0.1-3.7)	
Other	6	3 (25.0)	47.6 (1.6-1000.0)	.03	1 (7.7)	1.0		2 (10.5)	1.0	
Age at transplantation, y										
0-4	47	9 (75.0)	1.2 (0.1-11.4)	.88	11 (84.6)	Not estimated		17 (89.5)	Not estimated	
5-9	25	2 (16.7)	0.4 (0.03-5.8)	.52	2 (15.4)			2 (10.5)		
10-20	6	1 (8.3)	1.0		0			0		
Time since transplantation, y										
2-5	19	1 (8.3)	1.0		1 (7.7)	0.1 (0.01-1.5)	.11	0	Not estimated	
6-10	40	4 (33.3)	5.9 (0.3-133.5)	.26	7 (53.8)	0.6 (0.2-2.2)	.43	7 (36.8)		
≥11	19	7 (58.3)	31.7 (1.2-812.1)	.01	5 (38.5)	1.0		12 (63.2)		
Conditioning regimen										.36
TBI and chemotherapy	48	11 (91.7)	15.9 (1.3-199.4)	.03	5 (38.5)	1.0 (0.3-3.4)	>.99	10 (52.6)	0.6 (0.2-1.7)	
Chemotherapy only	30	1 (8.3)	1.0		8 (61.5)	1.0		9 (47.4)	1.0	
Chronic graft-vs-host disease										.87
Yes	9	1 (8.3)	0.6 (0.1-5.8)	.71	0	Not estimated		2 (10.5)	0.9 (0.2-4.6)	
No	69	11 (91.7)	1.0		13 (100.0)			17 (89.5)	1.0	
Major medical condition										.32
Yes	19	4 (33.3)	1.7 (0.4-6.4)	.43	4 (30.8)	1.4 (0.4-5.5)	.56	3 (15.8)		
No	59	8 (66.7)	1.0		9 (69.2)	1.0		16 (84.2)	1.0	

Abbreviations: CI, confidence interval; HCT, hematopoietic stem cell transplantation; OR, odds ratio; TBI, total body irradiation.

hood report a physical participation restriction that limits independence in personal care or routine activities, a significantly higher proportion than found in a comparison group of similar sex and age. Although few quantitative studies of physical and social participation restrictions in individuals who received HCT as children exist, our findings support previous work in the adult HCT population, where the prevalence of physical participation restrictions has been estimated at 9.5% to 26.3%.[19-21] In our relatively young adult population, the proportion of survivors married or living as married was also lower (26.8%) than reported by other researchers in popu-

©2005 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/23/2013

Table 5. Association Between Participation Restriction and Performance Limitation Among Survivors of Childhood HCT

Performance Limitation	Restricted Physical Participation OR* (95% CI)	Restricted Physical Participation *P* Value	Currently Married OR* (95% CI)	Currently Married *P* Value
Adults				
Physical performance limitation	22.1 (6.3-77.9)	.001	0.2 (0.1-0.9)	.03
Emotional performance limitation	17.1 (4.6-64.0)	.001	0.3 (0.1-1.7)	.17
Educational attainment				
Did not graduate from high school	4.7 (1.1-21.0)	.04	0.9 (0.1-5.0)	.92
High school graduate	1.0			
At least some college	0.1 (0.01-0.8)	.03	1.1 (0.5-2.4)	.89
	Restricted Social Participation			
Children				
Physical performance limitation	5.9 (0.9-40.1)	.09	4.9 (0.9-26.3)	.08
Emotional performance limitation	9.2 (1.2-68.0)	.03	83.3 (9.9-698.7)	.001
Required special education	10.1 (1.0-99.9)	.05	8.7 (1.6-48.3)	.01

Abbreviations: CI, confidence interval; HCT, hematopoietic stem cell transplantation; OR, odds ratio.
*The OR is the relative odds of having a participation restriction for those with a particular performance limitation compared with those without, adjusted for age at interview and time since transplantation.

lations of survivors who received HCT during adulthood (57.0%-71.0%).[22-25] Among child participants in our study, 16.7% had a reported difficulty with social skills. Another recent study[26] of childhood HCT survivors reported an even higher proportion (25.0%) who indicated difficulty with social skills.

In our study, physical participation restrictions and not being in a marital relationship were significantly associated with physical performance limitations, independent of effects of age, length of survival, sex, and race/ethnicity. Physical performance limitations were most common in young adult HCT survivors who had a major medical condition, cGVHD, or both. These findings are consistent with much of the literature related to late effects and quality of life in HCT recipients, which shows that physical symptoms and physical performance limitations continue to be a problem for a small proportion of long-term survivors.[3,19,27-34]

Among the child HCT survivors, our study demonstrated that physical and social participation restrictions were associated with limitations in physical and emotional performance and with the need for special education. Children who received TBI as part of their conditioning regimen were more likely to have impaired physical performance. Limitations in physical performance were more common in children with a longer survival time, perhaps indicating the loss of function over time. There is little information available about the effects of TBI on physical performance; however, TBI was previously reported to be associated with limitations in cognitive functioning in childhood HCT recipients.[35,36] Recent studies indicate that cognitive decline may not become apparent until later in the child's development.[37]

Methodologic limitations need to be considered when interpreting these results. First, given the relatively low response rate (60% of those successfully contacted), the possibility exists that participation bias influenced our estimates. Participants did not differ from nonparticipants by most sociodemographic or treatment factors, but we could not assess differences in medical late effects, performance limitations, or participation status. Second, our comparison group consisted of siblings of cancer survivors who are by nature indirect participants in the cancer experience and could conceivably have uncommonly high frequencies of performance limitations in the emotional or educational domains.[38,39] Third, sample size restrictions did not allow us to provide reliable statistical estimates of outcomes by type of cancer, specific conditioning regimen, transplantation type, or stem cell source. Fourth, the survey for the younger participants was completed by their parents, who may have expectations and interpretations that differ from those of their children in terms of both emotional performance and participation in social situations. Finally, because the data regarding medical late effects, performance limitations, and participation restrictions were collected simultaneously, we cannot be certain about the temporal association among these outcomes.

This study represents the first attempt, to our knowledge, to report in a comprehensive and systematic fashion the participation restrictions experienced by long-term cancer survivors who underwent transplantation during childhood. We have shown in this study that although most survivors lead independent and productive lives, a subset of individuals have persistent medical late effects or organ system impairments that result in performance limitations associated with impaired social skills, decreased physical independence, and decreased rates of marriage. Surveillance and long-term follow-up should include monitoring of children and adults treated during childhood who are at risk for functional loss so that they can be referred for intervention to restore function, provide compensatory strategies for function that cannot be restored, or adapt the environment to allow optimal participation in home and social environments.[40,41]

Accepted for Publication: February 17, 2005.
Correspondence: James G. Gurney, PhD, Division of General Pediatrics, University of Michigan, 300 N Ingalls, Room 6E08, Ann Arbor, MI 48109-0456 (jamegurn@umich.edu).

©2005 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/23/2013

Funding/Support: This study was supported by grant CA78938-02 from the National Institutes of Health, Bethesda, Md. Dr Bhatia is a Clinical Scholar of the Leukemia and Lymphoma Society, White Plains, NY. Dr Gurney receives support from the Children's Cancer Research Fund at the University of Minnesota.

REFERENCES

1. Horowitz MM. Uses and growth of hematopoietic cell transplantation. In: Blume KG, Forman SJ, Appelbaum FR, eds. *Thomas' Hematopoietic Cell Transplantation*. 3rd ed. Malden, Mass: Blackwell Publishing; 2004:9-15.
2. Socie G, Stone JV, Wingard JR, et al; Late Effects Working Committee of the International Bone Marrow Transplant Registry. Long-term survival and late deaths after allogeneic bone marrow transplantation. *N Engl J Med*. 1999;341:14-21.
3. Duell T, van Lint MT, Ljungman P, et al; EBMT Working Party on Late Effects and EULEP Study Group on Late Effects; European Group for Blood and Marrow Transplantation. Health and functional status of long-term survivors of bone marrow transplantation. *Ann Intern Med*. 1997;126:184-192.
4. Socie G, Stone JV, Wingard JR, et al; Late Effects Working Committee of the International Bone Marrow Transplant Registry. Long-term survival and late deaths after allogeneic bone marrow transplantation. *N Engl J Med*. 1999;341:14-21.
5. Flowers MED, Deeg HJ. Delayed complications after hematopoietic cell transplantation. In: Blume KG, Forman SJ, Appelbaum ER, eds. *Thomas' Hematopoietic Cell Transplantation*. 3rd ed. Malden, Mass: Blackwell Publishing; 2004: 944-961.
6. Guinan EC, Krance RA, Lehmann LF. Stem cell transplantation in pediatric oncology. In: Pizzo PA, Polack DG, eds. *Principles and Practice of Pediatric Oncology*. 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2000:429-452.
7. Cool VA. Long-term neuropsychological risks in pediatric bone marrow transplant: what do we know? *Bone Marrow Transplant*. 1996;18(suppl 3):S45-S49.
8. Kramer JH, Crittenden MR, DeSantes K, Cowan MJ. Cognitive and adaptive behavior 1 and 3 years following bone marrow transplantation. *Bone Marrow Transplant*. 1997;19:607-613.
9. Phipps S, Dunavant M, Srivastava DK, Bowman L, Mulhern RK. Cognitive and academic functioning in survivors of pediatric bone marrow transplantation. *J Clin Oncol*. 2000;18:1004-1011.
10. Andrykowski MA, Altmaier EM, Barnett RL, Burish TG, Gingrich R, Henslee-Downey PJ. Cognitive dysfunction in adult survivors of allogeneic marrow transplantation: relationship to dose of total body irradiation. *Bone Marrow Transplant*. 1990;6:269-276.
11. Meyers CA, Weitzner M, Byrne K, Valentine A, Champlin RE, Przepiorka D. Evaluation of the neurobehavioral functioning of patients before, during, and after bone marrow transplantation. *J Clin Oncol*. 1994;12:820-826.
12. Peper M, Steinvorth S, Schraube P, et al. Neurobehavioral toxicity of total body irradiation: a follow-up in long-term survivors. *Int J Radiat Oncol Biol Phys*. 2000; 46:303-311.
13. Harder H, Cornelissen JJ, Van Gool AR, Duivenvoorden HJ, Eijkenboom WM, van den Bent MJ. Cognitive functioning and quality of life in long-term adult survivors of bone marrow transplantation. *Cancer*. 2002;95:183-192.
14. Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol*. 2002;38:229-239.
15. Louie AD, Robison LL, Bogue M, Hyde S, Forman SJ, Bhatia S. Validation of self-reported complications by bone marrow transplantation survivors. *Bone Marrow Transplant*. 2000;25:1191-1196.
16. Derogatis LR. *Brief Symptom Inventory (BSI) 18, Administration, Scoring, and Procedures Manual*. Minneapolis, Minn: NCS Pearson Inc; 2000.
17. Achenbach TM, Ruffle TM. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatr Rev*. 2000; 21:265-271.
18. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA*. 2003;290:1583-1592.
19. Broers S, Kaptein AA, Le Cessie S, Fibbe W, Hengeveld MW. Psychological functioning and quality of life following bone marrow transplantation: a 3-year follow-up study. *J Psychosom Res*. 2000;48:11-21.
20. Bush NE, Haberman M, Donaldson G, Sullivan KM. Quality of life of 125 adults surviving 6-18 years after bone marrow transplantation. *Soc Sci Med*. 1995; 40:479-490.
21. Molassiotis A, Boughton BJ, Burgoyne T, van den Akker OB. Comparison of the overall quality of life in 50 long-term survivors of autologous and allogeneic bone marrow transplantation. *J Adv Nurs*. 1995;22:509-516.
22. Prieto JM, Saez R, Carreras E, et al. Physical and psychosocial functioning of 117 survivors of bone marrow transplantation. *Bone Marrow Transplant*. 1996; 17:1133-1142.
23. Belec RH. Quality of life: perceptions of long-term survivors of bone marrow transplantation. *Oncol Nurs Forum*. 1992;19:31-37.
24. Baker F, Curbow B, Wingard JR. Role retention and quality of life of bone marrow transplant survivors. *Soc Sci Med*. 1991;32:697-704.
25. Sutherland HJ, Fyles GM, Adams G, et al. Quality of life following bone marrow transplantation: a comparison of patient reports with population norms. *Bone Marrow Transplant*. 1997;19:1129-1136.
26. Nespoli L, Verri AP, Locatelli F, Bertuggia L, Taibi RM, Burgio GR. The impact of paediatric bone marrow transplantation on quality of life. *Qual Life Res*. 1995; 4:233-240.
27. Felder-Puig R, Peters C, Matthes-Martin S, et al. Psychosocial adjustment of pediatric patients after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 1999;24:75-80.
28. Hjermstad MJ, Evensen SA, Kvaloy SO, Fayers PM, Kaasa S. Health-related quality of life 1 year after allogeneic or autologous stem-cell transplantation: a prospective study. *J Clin Oncol*. 1999;17:706-718.
29. Heinonen H, Volin L, Uutela A, Zevon M, Barrick C, Ruutu T. Quality of life and factors related to perceived satisfaction with quality of life after allogeneic bone marrow transplantation. *Ann Hematol*. 2001;80:137-143.
30. Bush NE, Donaldson GW, Haberman MH, Dacanay R, Sullivan KM. Conditional and unconditional estimation of multidimensional quality of life after hematopoietic stem cell transplantation: a longitudinal follow-up of 415 patients. *Biol Blood Marrow Transplant*. 2000;6:576-591.
31. Kiss TL, Abdolell M, Jamal N, Minden MD, Lipton JH, Messner HA. Long-term medical outcomes and quality-of-life assessment of patients with chronic myeloid leukemia followed at least 10 years after allogeneic bone marrow transplantation. *J Clin Oncol*. 2002;20:2334-2343.
32. Chiodi S, Spinelli S, Ravera G, et al. Quality of life in 244 recipients of allogeneic bone marrow transplantation. *Br J Haematol*. 2000;110:614-619.
33. Lee SJ, Fairclough D, Parsons SK, et al. Recovery after stem-cell transplantation for hematologic diseases. *J Clin Oncol*. 2001;19:242-252.
34. Syrjala KL, Chapko MK, Vitaliano PP, Cummings C, Sullivan KM. Recovery after allogeneic marrow transplantation: prospective study of predictors of long-term physical and psychosocial functioning. *Bone Marrow Transplant*. 1993;11: 319-327.
35. Smedler AC, Bolme P. Neuropsychological deficits in very young bone marrow transplant recipients. *Acta Paediatr*. 1995;84:429-433.
36. Smedler AC, Nilsson C, Bolme P. Total body irradiation: a neuropsychological risk factor in pediatric bone marrow transplant recipients. *Acta Paediatr*. 1995; 84:325-330.
37. Sattler J. *Assessment of Children*. 4th ed. San Diego, Calif: Jerome M. Sattler; 2001.
38. Sahler OJ, Roghmann KJ, Carpenter PJ, et al. Sibling adaptation to childhood cancer collaborative study: prevalence of sibling distress and definition of adaptation levels. *J Dev Behav Pediatr*. 1994;15:353-366.
39. Sloper P, While D. Risk factors in the adjustment of siblings of children with cancer. *J Child Psychol Psychiatry*. 1996;37:597-607.
40. Dimeo F, Bertz H, Finke J, Fetscher S, Mertelsmann R, Keul J. An aerobic exercise program for patients with haematological malignancies after bone marrow transplantation. *Bone Marrow Transplant*. 1996;18:1157-1160.
41. Wingard JR. Quality of life following bone marrow transplantation. *Curr Opin Oncol*. 1998;10:108-111.

©2005 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/23/2013