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ORIGINAL REPORT

Long-Term Health-Related Quality of Life, Growth, and Spiritual Well-Being After Hematopoietic Stem-Cell Transplantation

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ABSTRACT

Purpose
To examine health-related quality of life (HRQOL) and growth, and spiritual well-being in adult survivors of hematopoietic stem-cell transplantation (HSCT) for a malignant disease.

Methods
HSCT survivors (n = 662) were recruited through the International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry and were drawn from 40 transplantation centers. HSCT survivors completed a telephone interview and a set of questionnaires a mean of 7.0 years post-HSCT (range, 1.8 to 22.6 years). Study measures included a variety of standardized measures of HRQOL and growth and spiritual well-being. An age- and sex-matched healthy comparison (HC) group (n = 158) was recruited using a peer nomination method. The HC group completed a parallel telephone interview and set of questionnaires.

Results
Multivariate analysis of variance analyses found the HSCT survivor group reported poorer status relative to the HC group for all HRQOL outcome clusters including physical health, physical functioning, social functioning, psychological adjustment, and dyadic adjustment. In contrast, the HSCT survivor group reported more psychological and interpersonal growth. Mean effect size for the 24 outcome indices examined was 0.36 standard deviations, an effect size often considered clinically meaningful or important. The largest group differences were found for measures of general health, physical function and well-being, depression, cognitive function, and fatigue.

Conclusion
The experience of HSCT for a malignant disease has a wide-ranging, longstanding, and profound impact on adult recipients. Relative to healthy controls, HSCT survivors reported poorer physical, psychological, and social functioning but, conversely, more psychological and interpersonal growth, differences that appeared to persist many years after HSCT.

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INTRODUCTION

Although hematopoietic stem-cell transplantation (HSCT) has been successfully used to treat various malignant and nonmalignant, typically life-threatening diseases, HSCT is associated with risk for significant physical and psychosocial morbidity. Transplantation-related morbidity is evident throughout the course of HSCT, beginning with pretransplantation conditioning and extending well into the post-transplantation recovery phase. Recognition of this spectrum of physical and psychosocial late effects has been accompanied by realization that for many HSCT survivors, cure or control of their underlying disease may not be accompanied by a restoration of health. Accordingly, the health-related quality of life

(HRQOL) of HSCT survivors has emerged as a significant area of study.[1-3]

HRQOL is the extent to which usual or expected physical, emotional, and social well-being are affected by a medical condition or its treatment.[4] HRQOL assessment requires attention to several dimensions, including physical concerns (eg, symptoms), functional ability, family well-being, emotional well-being, sexuality, and social functioning.[5] Studies of HRQOL, both in the general context of malignant disease and the specific context of HSCT, have focused on elucidation of deficits in physical, social, and emotional well-being associated with cancer and cancer treatment. However, this ignores the possibility that psychological, interpersonal, and spiritual well-being might be positively affected by the disease and treatment experience.[6-8]

The possibility that the experience of life-threatening, malignant disease might yield both negative and positive outcomes has an empirical and theoretical foundation. Research has established cancer survivors, including HSCT survivors, often report their disease experience has improved interpersonal relationships, enhanced appreciation for life, reordered life priorities, increased empathy and self-esteem, or deepened spirituality.[6,9-13] Theoretically, the emergence of positive sequelae might be understood in terms of post-traumatic growth[14,15] because life-threatening disease and treatment can be viewed as a traumatic stressor. Although trauma exposure can trigger negative sequelae (eg, distress, social estrangement), adaptation to trauma can result in new modes of thought and behavior that represent improvements from pretrauma status (ie, growth).[6,7,14-18]

Although post-HSCT HRQOL has been the focus of many separate investigations,[19-27] our study extends this research in several respects. First, our study includes measures of post-traumatic growth and spiritual well-being in its assessment of post-HSCT outcomes and is thus able to provide a more comprehensive portrayal of the impact of HSCT. Second, our study includes a large sample ($n > 500$) of HSCT survivors drawn from 40 HSCT centers. Prior studies of post-HSCT HRQOL have included survivors from a single institution, or at most, several institutions. Few studies have included more than 300 survivors. Given that transplantation centers differ with regard to case mix and supportive services, the large multicenter nature of this study enhances the generalizability of our findings. Finally, this study collects HRQOL information from a matched, comparison group of healthy individuals. A healthy comparison (HC) group has been included in only one previous investigation of HRQOL in HSCT survivors[28,29]; that study included only 43 recipients of autologous HSCT for breast cancer and focused on a limited set of HRQOL end points. Other studies have compared survivors' HRQOL to those of population norms,[26] but such comparisons can be misleading if the norm group is dissimilar to the HSCT survivor group on critical variables such as age, sex, or education. Inclusion of a matched, HC group enables the HRQOL status of HSCT survivors to be placed in its appropriate context, enabling a more precise determination of the impact of HSCT.

METHODS

Subjects and Procedures

All procedures were implemented after approval for use of human subjects from the local institutional review board of all participating transplantation centers. HSCT survivors who were potential participants at participating transplantation centers were identified from records of the International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry (IBMTR/ABMTR). Patients were eligible for the survivor group if they had HSCT at $\geq$ 18 years of age, had a single allogeneic or autologous HSCT, were $\geq$ 12 months post-HSCT for one of four malignant diseases (chronic myelogenous leukemia, acute leukemia, lymphoma, or breast cancer), were in continuous remission since HSCT, and were able to read and understand English.

Between March 2000 and September 2002, 2,447 individuals at 40 transplantation centers were identified from IBMTR/ABMTR records as eligible for the survivor group. Patients meeting the first three eligibility criteria at each transplantation center were stratified by diagnosis, transplant type (autologous *v* allogeneic), years post-HSCT (< 5 *v* ≥ 5 years), and intensity of pretransplantation cytotoxic treatment (low *v* high). A stratified list of eligible survivors at each center was used to select survivors randomly; each center contacted these survivors to determine interest in participation. If patients were interested, study eligibility was verified and consent forms were mailed or given to the survivor for signature, and returned to the HSCT center. Once written consent was received, the HSCT center forwarded contact information for that survivor to the Center on Outcomes, Research and Education (CORE) at Evanston Northwestern Healthcare Center (Evanston, IL). Research staff at CORE then contacted the survivor, scheduled a telephone interview, and mailed a packet of questionnaires for completion and return by mail. On completion of the telephone interview and questionnaire packet, clinical information was abstracted from IBMTR/ABMTR records. Specific information included date and type of initial cancer diagnosis and date and type of HSCT, including the nature of the donor relationship for allogeneic recipients. HSCT respondents were paid $20 for participation.

During the telephone interview, each member of the survivor group was asked to nominate three to five acquaintances, similar to them in age, education, and sex, to participate in an HC group. Eligibility criteria for the HC group were $\geq$ 18 years of age; no history of HSCT or malignant disease; matched on sex, age ($\pm$ 5 years), partner status (partnered *v* not partnered), and education ($\pm$ 2 years) with a member of the survivor group; ability to read and understand English; and neither involved in providing care to the HSCT survivor after their HSCT nor profoundly emotionally affected by the survivor's HSCT experience.

Using this approach, 1,179 potential participants in the HC group were identified. If an HSCT survivor nominated more than one individual for the HC group, one was chosen at random and contacted by telephone by CORE staff. Study eligibility was confirmed and study procedures described. Those interested in participation were mailed consent forms for completion and return by mail. On receipt of a signed consent form, CORE staff contacted

the individual by telephone, scheduled a telephone interview, and mailed a set of questionnaires for completion and return by mail. If the first individual contacted did not meet eligibility criteria or was not interested in participation, another individual was randomly selected from the nominees provided by the HSCT survivor. If no match could be found from the list of acquaintances furnished by the HSCT survivor, then a potential match was selected from the larger, unused pool of acquaintances furnished by the survivor group as a whole. This process was repeated until a match was found for every third member of the HSCT survivor group. HC respondents were paid $20 for participation.

Study Measures

Study measures assessed various domains including demographic, growth and spiritual well-being, general health perceptions, psychological adjustment, physical functioning, and social functioning. Administration of the entire set of study measures was about equally divided between a telephone interview and a questionnaire packet. With only minor exceptions, the survivor and HC groups completed identical study measures in the telephone interview and questionnaire packet.

Demographic information. Information obtained included age, race, marital status, education, and annual household income.

General health perception. Measures included the general health perception subscale of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36-GH)[30] and the Perceived Health Questionnaire (PHQ).[6] The PHQ obtains separate ratings of current health, past health, and health of a typical person of the same age as the participant using a 10-point Likert scale with end points labeled poor health and excellent health. Ratings of past health for the survivor group were made with reference to their health before cancer diagnosis. For the HC group, ratings of past health were made with reference to a point in time corresponding to cancer diagnosis for their matched counterpart in the survivor group.[6] Two PHQ indices were computed. PHQ-Comparative Health was defined as the difference between ratings of current health and health of a typical person, whereas PHQ-Health Change was defined as the difference between ratings of current health and past health. Negative values for the Comparative Health and Health Change indices thus indicate current health is poorer than the health of a typical person and poorer than prior health, respectively.

Psychological adjustment. Measures included the Trait Anxiety subscale of the Spielberger State-Trait Anxiety Inventory (STAI-Trait),[31] the mental health subscale of the SF-36 (SF-36-MH),[30] and the Center for Epidemiologic Studies Depression Scale (CES-D).[32] The CES-D yields a total score and a dichotomous index of likely cases of clinically significant depressive symptoms based on a cutoff score of ≥ 16.[33]

Physical functioning. Measures included the Physical Functioning (SF-36-PF) and Pain (SF-36-Pain) subscales of the SF-36,[30] the Physical Well-Being subscale of the Functional Assessment of Cancer Therapy scale (FACT-PWB),[34] the Functional Assessment of Cancer Illness Therapy Fatigue subscale (FACIT-Fatigue),[35] the Medical Outcomes Study Sexual Problems (MOS-Sex)[36] and Sleep Problems (MOS-Sleep)[37] scales, and the Alertness Behavior subscale of the Sickness Impact Profile (SIP-AB).[38] The SIP is a measure of illness-related functional status. Specifically, the SIP-AB subscale is a measure of mild to moderate cognitive dysfunction and consists of 10 items assessing the presence of difficulties in memory, attention, concentration, and cognitive processing. It has been used in prior research examining cognitive dysfunction in survivors of allogeneic marrow transplantation.[39]

Social functioning. Measures included the Social Functioning subscale of the SF-36 (SF-36-SF),[30] the Medical Outcomes Study Family Functioning scale (MOS-Family),[40] and total scores on the Duke-University of North Carolina Social Support scale[41] and University of California, Los Angeles Loneliness scale.[42] Respondents with a current partner completed the Dyadic Adjustment Scale (DAS).[43] The DAS consists of 32 items and is a widely used measure of satisfaction and adjustment in marital or committed couple relationships.[44-45] The DAS yields a total score and subscale scores for Consensus, Affectional Expression, Cohesion, and Satisfaction.

Growth or spiritual-well being. Measures included the Posttraumatic Growth Inventory (PTGI)[46] and the Spiritual Well-Being subscale of the Functional Assessment of Cancer Illness Therapy scale (FACIT-Sp).[47] The PTGI assesses growth or benefits after a specific traumatic event. For the survivor group, the PTGI was keyed to "as a result of having had cancer or cancer treatment such as a blood or marrow transplant." As in previous research investigating positive psychosocial change[6] or post-traumatic growth[10] after cancer diagnosis and treatment, the HC group completed the PTGI with reference to change occurring over the same span of time since cancer diagnosis for their matched counterpart in the survivor group. This enables identification of the extent of reported positive change or growth attributable to the cancer experience as opposed to the simple passage of time. Total scores were calculated for both the PTGI and FACIT-Sp.

Statistical Analysis

For each of our six outcome clusters, a multivariate analysis of variance (MANOVA) was conducted with scale and subscale scores within each cluster used as dependent variables. Group (survivor or HC), sex, and education (three levels) were included as the independent variables in the model for each outcome cluster. For outcome clusters yielding a significant multivariate group effect, univariate (analysis of variance [ANOVA]) models subsequently were fit to each dependent variable within that cluster, with sex and education used as covariates. The studentized residuals of these models were studied for assumption violations. The criterion for statistical significance was .05.

RESULTS

A flow chart summarizing recruitment of HSCT survivors is shown in Fig 1. A total of 2,447 potentially eligible survivors were identified from IBMTR/ABMTR records; 1,946 were randomly selected for potential study enrollment. Of these, 295 were ineligible, primarily due to death (n = 133) or disease relapse (n = 134), and contact information was unavailable for 262. An attempt was made to contact the remaining 1,399 survivors; contact was made with 960 survivors. Of these, 118 declined participation and 138 provided verbal consent but did not return a consent form. The remaining 704 HSCT survivors (73.3% of eligible survivors successfully contacted) provided written consent. Of these, 42 were withdrawn from the study for various reasons including voluntary withdrawal (n = 16), study ineligibility,

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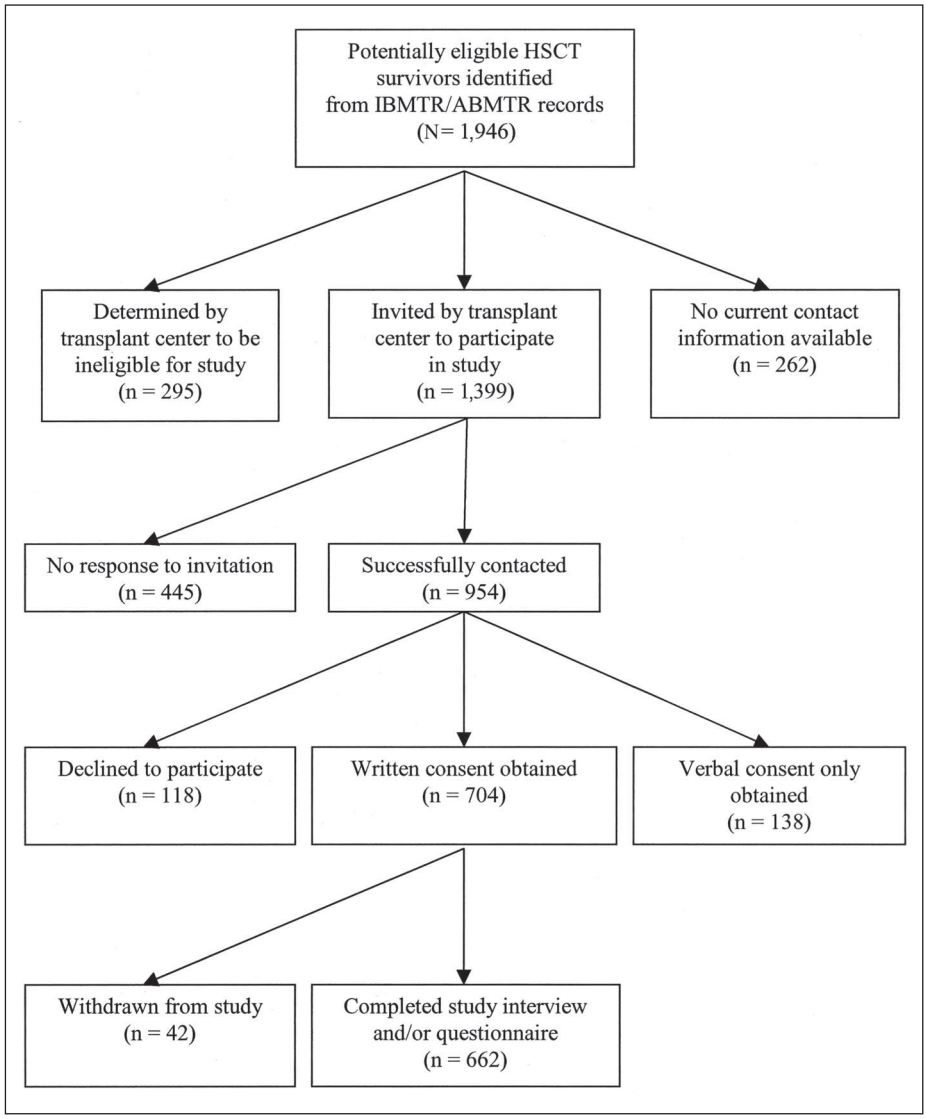

Fig 1. Flow chart summarizing recruitment of the hematopoietic stem-cell transplantation (HSCT) survivor group. IBMTR/ABTR, International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry.

(n = 12), or loss to follow-up (n = 10). Of the remaining 662, 636 completed the interview and questionnaires, 23 completed only the interview, and three completed only questionnaires. Survivors completing both portions of the study were compared with those completing only one portion on demographic, clinical, and psychosocial variables, and few differences emerged. Thus all 662 respondents were retained in the survivor group in all analyses. Tables 1 and 2 list clinical and demographic characteristics for the survivor group.

A total of 1,179 acquaintances were nominated for the HC group. Of these, 631 were selected for contact and screening for eligibility, with 177 ultimately contacted and deemed eligible. Of these 177 study eligible individuals, 159 provided written consent (90%). Of these, 151 completed the interview and questionnaires, five completed only questionnaires, and two completed only the interview. All 158 respondents were retained as the HC group. Table 2 lists demographic characteristics for the HC group. Comparison of the survivor and HC groups found no differences for age ($t_{816} = 1.09$; not significant [ns]), sex ($\chi^2_1 = 3.13$; ns), or race or ethnicity ($\chi^2_1 = 1.73$; ns). The two groups did differ on annual income ($\chi^2_4 = 13.07$; $P < .05$) and current partner status ($\chi^2_1 = 13.40$; $P < .001$), with the survivor group more likely to be single and report a lower income. There was a trend toward a difference in education ($\chi^2_4 = 9.36$; $P = .053$), with the survivor group demonstrating less education. Because differences in partner status may be a result of diagnosis and treatment, only education was used as a covariate in subsequent analyses.

Fifty-seven respondents did not complete enough items on one or more questionnaires to compute appropriate scale and subscale scores. Comparison of these 57 respondents with the remaining 763 respondents with

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Table 1. Clinical Characteristics for Survivor Group (n = 662)

Characteristic	No. of Patients	%
Time since HSCT, years		
Mean	7.0	
SD	3.1	
Median	6.6	
Range	1.8-22.6	
Type of transplant		
Allogeneic HSCT	267	41
Autologous HSCT	386	59
Missing data	9	1
Donor relationship (allogeneic HSCT only)		
HLA-identical sibling	187	70
Alternative related donor	11	4
Unrelated donor	33	12
Other or missing	36	13
Malignant disease at initial diagnosis		
AML	194	29
CML	128	19
ALL	44	7
Breast cancer	154	23
Hodgkin's or non-Hodgkin's lymphoma	131	20
Other	2	1
Missing data	9	1

NOTE. Some percentages may not total 100% because of rounding.
Abbreviations: HSCT, hematopoietic stem-cell transplantation; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; ALL, acute lymphocytic leukemia.

Table 2. Demographic Characteristics for Survivor (n = 662) and HC (n = 158) groups

Variable	Survivor Group (%)	HC Group (%)
Age, years		
Mean	49.1	50.1
SD	10.3	14.2
Range	21-77	27-76
Education*		
< High school graduate	5	1
High school graduate	24	18
Some college or technical education	32	32
College degree	19	23
> College degree	20	26
Occupational status†		
Working or student	73	75
Not working	15	5
Retired	11	20
Married or partnered†	73	87
White	92	95
Male*	38	30
Annual family income‡		
< $20,000	11	3
$20,000-$40,000	22	15
$40,000-$60,000	24	27
$60,000-$80,000	15	20
> $80,000	28	34

NOTE. Percentages shown represent the percentage of respondents with nonmissing data for that variable. Some percentages may not total 100% because of rounding.
Abbreviations: HC, healthy comparison; M, mean; SD, standard deviation.
*$P < .10$.
†$P < .001$.
‡$P < .05$.

complete questionnaire data suggested no differences on demographic and clinical variables. We thus considered missing data to be random. Multiple imputation methods were used to impute any missing data, and the last of five imputed datasets were used in all analyses.

Comparison of Survivor and HC Groups

Physical health. The physical health cluster consisted of four variables: the SF-36-GH subscale score and PHQ ratings of current health, health change, and comparative health. MANOVA results indicated a significant group effect ($F = 25.01$; $P < .001$). Univariate ANOVAs revealed significant group effects for all four variables. The survivor group reported poorer SF-36-GH subscale scores, poorer PHQ ratings of current health, and viewed their current health as worse than a typical person their age and worse than their health before cancer diagnosis. Group means, SEs, and effect sizes for physical health variables are listed in Table 3.

Physical functioning. The physical functioning cluster consisted of seven variables: scores on the SF-36-Pain and SF-36-PF subscales, MOS-Sexual and MOS-Sleep Problems scales, SIP-AB subscale, FACT-PWB subscale, and the FACIT-Fatigue scale. MANOVA results indicated a significant group effect ($F = 12.35$; $P < .001$). Univariate ANOVAs revealed significant group effects for all seven variables. The survivor group reported more sleep and sexual problems, poorer physical functioning (SF-36) and well-being (FACT), greater fatigue (FACIT), more pain (SF-36), and more cognitive dysfunction (SIP). Group means, SEs, and effect sizes for physical functioning variables are listed in Table 3.

Psychological adjustment. The psychological adjustment cluster consisted of three variables: CES-D, STAI-Trait, and SF-36-MH subscale scores. MANOVA results indicated a significant group effect ($F = 15.10$; $P < .001$). Univariate ANOVAs revealed significant group effects for all variables. The survivor group reported more depressive symptoms, trait anxiety, and poorer mental health. Group means, SEs, and effect sizes for psychological adjustment variables are listed in Table 3.

The proportion of potentially clinically significant cases of depressive symptoms in the survivor and HC groups was compared using χ^2 test. Using the CES-D cutoff score of ≥ 16 to define cases, the proportion of cases in the survivor group (30%) was greater than in the HC group (8%; $P < .0001$).

Table 3. Adjusted Means, Standard Errors, Mean Group Differences, and Effect Sizes for HSCT Outcome Clusters

Cluster or Variable	Survivor Group M*	Survivor Group SE	HC Group M*	HC Group SE	Difference†	SD‡	Effect Size§	α‖	P¶
Physical Health									
SF-36-General Health	60.7	0.90	76.0	1.84	15.3	23.4	−0.65	.83	< .001
PHQ-Current Health	7.3	0.06	7.9	0.13	0.6	1.6	−0.35	—	< .001
PHQ-Comparative Health	−0.9	0.07	0.3	0.15	1.3	1.9	−0.66	—	< .001
PHQ-Health Change	−1.3	0.09	−0.8	0.18	0.5	2.3	−0.20	—	.021
Psychological Adjustment									
CES-Depression	11.7	0.38	6.3	0.79	5.4	9.9	−0.54	.92	< .001
STAI-Anxiety	37.2	0.41	34.5	0.84	2.7	10.4	−0.26	.93	.003
SF-36-Mental Health	75.9	0.70	82.3	1.43	6.4	17.7	−0.36	.85	< .001
Social Function									
Duke-Social Support	31.8	0.27	32.5	0.55	0.7	6.7	−0.10	.88	.269
MOS-Family Function	70.2	0.96	72.1	1.97	2.0	24.0	−0.08	.92	.362
UCLA-Loneliness	38.9	0.40	37.6	0.82	1.4	10.0	−0.14	.93	.121
SF-36-Social Function	80.4	0.93	90.1	1.90	9.7	23.7	−0.41	.83	< .001
Physical Function									
SF-36-Pain	70.2	0.98	75.0	2.00	4.9	24.8	−0.20	.92	.026
SF-36-Physical Function	73.8	0.96	86.7	1.97	12.9	24.9	−0.52	.92	< .001
MOS-Sleep Problems	20.2	0.26	17.6	0.54	2.6	6.6	−0.39	.76	< .001
MOS Sexual Problems	33.6	1.28	20.0	2.61	13.7	32.4	−0.42	.90	< .001
SIP-Alertness Behavior	2.6	0.11	0.9	0.22	1.7	2.8	−0.60	.83	< .001
FACT-Physical Well-Being	22.6	0.21	25.6	0.42	3.0	5.3	−0.57	.84	< .001
FACIT-Fatigue	36.9	0.44	42.6	0.90	5.7	11.3	−0.50	.94	< .001
Growth and Spiritual Well-Being									
PTGI-Total	66.3	0.82	57.5	1.67	8.8	21.1	0.42	.94	< .001
FACIT-Spiritual Well-Being	35.9	0.34	37.4	0.70	1.5	8.6	−0.17	.88	.054

NOTE. Negative effect sizes indicate survivor group reported poorer status than HC group.
Abbreviations: HSCT, hematopoietic stem-cell transplantation; HC, healthy comparison; M, mean; SD, standard deviation; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; PHQ, Perceived Health Questionnaire; CES, Center for Epidemiologic Studies; STAI, Spielberger State-Trait Anxiety Inventory; MOS, Medical Outcomes Study; UCLA, University of California Los Angeles; SIP, Sickness Impact Profile; FACT, Functional Assessment of Cancer Therapy; FACIT, Functional Assessment of Cancer Illness Therapy; PTGI, Posttraumatic Growth Inventory.
*Least squares mean from linear model including gender and education.
†Difference between adjusted group means.
‡Standard deviation of survivor and HC groups combined.
§Difference/SD.
‖Cronbach's alpha reliability coefficient.
¶Test of mean difference between survivor and HC groups.

Social functioning. The social functioning cluster consisted of four variables: scores on the DUKE-SS; MOS-Family Functioning; University of California Los Angeles Loneliness scales; and the SF-36-SF subscale. MANOVA results indicated a significant group effect ($F = 5.54$; $P < .001$). Univariate ANOVAs indicated a significant group effect for SF-36-SF scores ($P < .001$), with the survivor group reporting poorer social functioning. Group means, SEs, and effect sizes for social functioning variables are listed in Table 3.

Group differences in social functioning were also identified by examining the four subscale scores on the DAS. Analyses were based on 601 respondents (n = 129 for HC group; n = 472 for survivor group) who reported a current partner. MANOVA analysis indicated a significant group effect ($F = 2.89$; $P < .05$). Univariate ANOVAs indicated significant group effects for the Consensus, Satisfaction, and Affectional Expression subscales (all $P < 0.01$). The survivor group reported less consensus, less satisfaction, and less affectional expression in their marital or partner relationship. Group means, SEs, and effect sizes for the DAS subscales are listed in Table 4.

Growth and spiritual well-being. This cluster consisted of total scores for the PTGI and FACIT-Sp scales. MANOVA analysis yielded a significant group effect ($F = 17.54$; $P < .001$). Univariate ANOVAs indicated a significant group effect for PTGI score ($P < .001$), with the survivor group reporting more growth. The group effect for FACIT-Sp scores narrowly missed statistical significance ($P = .054$), with the survivor group reporting poorer spiritual well-being. Group means, SEs, and effect sizes for growth or spiritual well-being variables are listed in Table 3.

DISCUSSION

Results provide clear evidence that the experience of HSCT has a wide-ranging, longstanding, and profound impact,

Table 4. Adjusted Means, SEs, Mean Group Differences, and Effect Sizes for DAS Subscale Scores

Variable	Survivor Group (n = 472)		HC Group (n = 129)						
	M*	SE	M*	SE	Difference†	SD‡	Effect Size§	α‖	P¶
DAS-Consensus	47.9	0.40	50.6	0.77	2.6	8.6	−0.31	.91	.002
DAS-Satisfaction	38.2	0.33	40.4	0.65	2.2	7.2	−0.31	.90	.002
DAS-Cohesion	15.7	0.20	16.5	0.38	0.8	4.3	−0.18	.84	.061
DAS-Affectional Expression	8.1	0.13	8.8	0.25	0.7	2.7	−0.27	.72	.006

NOTE. Negative effect sizes indicate survivor group reported poorer status than HC group.
Abbreviations: DAS, Dyadic Adjustment Scale; HC, healthy comparison; SD, standard deviation.
*Least squares mean from linear model including gender and education.
†Difference between adjusted group means.
‡Standard deviation of survivor and HC groups combined.
§Difference/SD.
‖Cronbach's α reliability coefficient.
¶Test of mean difference between survivor and HC groups.

both positive and negative, on HSCT recipients. The impact was wide ranging because significant multivariate differences between the survivor and HC groups were evident for each of our six outcome clusters. The impact of HSCT was longstanding because group differences were evident even though our survivors were assessed a median of 6.6 years post-HSCT. Finally, the impact of HSCT was profound because the mean effect size across our 24 individual outcome variables exceeded one third of a standard deviation ([SD]mean, 0.36 SD), which is an effect size often considered clinically meaningful or important.[48-50]

Study results were remarkable for their consistency. HSCT survivors reported a consistent pattern of deficits on a spectrum of commonly used indices of HRQOL, spanning domains of physical, psychological, social, and dyadic functioning while simultaneously reporting enhanced status on the PTGI, an index of growth across psychological, interpersonal, and spiritual domains. These findings are not as paradoxical as they seem. Theoretical views of adaptation to traumatic stressors emphasize the dual potential for negative (eg, distress) and positive (eg, growth) outcomes.[6,14-16] Because of its aggressive nature and the life-threatening context in which it occurs, HSCT recipients are likely to experience it as a traumatic stressor.[8] Thus, the potential for post-traumatic growth is high in HSCT recipients. Combined with the potential for a spectrum of debilitating physical late effects[51-54] and the ever-present risk of recurrence or diagnosis of a second malignancy,[55-57] it is not surprising that HSCT survivors report deficits in HRQOL while simultaneously reporting positive psychological, interpersonal, and spiritual change (ie, growth). Of course, there are likely limits to this juxtaposition of positive and negative outcomes in HSCT recipients. On one hand, trauma adaptation theory would suggest recipients who did not regard their HSCT experience as sufficiently traumatic or life threatening are unlikely to report growth outcomes. Given that we did not assess whether recipients' perceived their HSCT experience as traumatic or threatening, we were unable to test this hypothesis. On the other hand, recipients who are severely traumatized by their experience and are plagued by severe deficits in physical, psychological, and social functioning are also unlikely to report growth outcomes.

Given the permanence of many physical late effects attributed to HSCT and the present risk for recurrence and diagnosis of a second malignancy, it is not surprising that HSCT survivors continued to report HRQOL deficits many years after HSCT. Noteworthy, however, was that HSCT survivors also reported more positive or growth outcomes many years after HSCT. Correlational analyses found no significant relationship between time post-HSCT and PTGI total score. Although the cross-sectional study design limits conclusions about the temporal trajectory of such positive growth outcomes, we believe our data strongly suggest such outcomes are not simply ephemeral. Although we hesitate to conclude HSCT is associated with permanent psychological growth, our data do suggest that positive outcomes continue to be reported many years after transplantation.

The mean effect size across all 24 of our outcome indices was 0.36 SD units, a medium effect size.[58] This effect size is in the 0.3 to 0.5 SD range, which is often considered a clinically important or meaningful difference.[48-50] Although it is impressive, this effect size obscures differences in effect size across outcome clusters and across variables within clusters. Specifically, the survivor and HC groups differed most on the physical health (mean effect size, 0.47 SD) and physical functioning clusters (mean effect size, 0.46 SD), while differing least on social functioning (mean effect size, 0.18 SD) and dyadic adjustment (mean effect size, 0.27 SD) clusters. Although differences on the psychological adjustment (mean effect size, 0.39 SD) and growth and spiritual well-being (mean effect size, 0.30 SD) clusters fell in between, the mean effect size for both these clusters also qualified as clinically important or meaningful. Using Cohen's effect size criteria,[58] one might conclude that the impact of

HSCT is medium to large in the physical domain, medium in the psychological domain, and medium to small in the social domain.

Furthermore, within our outcome clusters, certain variables yielded greater discrimination between the survivor and HC groups. Applying the effect size criterion of 0.3 to 0.5 SD noted above, group differences on 15 of 24 outcome variables would be considered clinically meaningful or important. All six of our outcome clusters are represented among these 15 variables, suggesting the breadth and depth of the impact of HSCT on HRQOL. Again, the adverse impact of HSCT appears to be most profound in the physical health and physical functioning outcome clusters, with effect sizes for nine of 11 variables in these clusters qualifying as meaningful or important differences. Conversely, the mean difference between the survivor and HC groups for PTGI total score also exceeded 0.3 SD, suggesting the growth reported by HSCT survivors was not only statistically significant but also clinically important or meaningful.

Approximately half of the 15 individual variables (n = 7) showing clinically meaningful or important differences yielded effect sizes exceeding 0.5 SD. This group included the SF-36-GH subscale (0.65 SD), the PHQ-Comparative Health index (0.66 SD), the SIP-AB subscale (0.60 SD), the FACT-PWB subscale (0.57 SD), the CES-D scale (0.54), the SF-36-PF subscale (0.52), and the FACIT-Fatigue subscale (0.50 SD). These results confirm previous research suggesting the deleterious impact of HSCT on physical health and functioning,[1-3,19,27] and confirm fatigue,[22,24,28,59] cognitive impairment,[60-61] and depression as significant HRQOL-related late effects.

Our findings also suggested specific outcome indices that appeared to be relatively less affected by HSCT. All three of these indices fell within the social functioning cluster and included the MOS-Family Function (effect size, 0.08 SD), DUKE-Social Support (effect size, 0.10 SD), and University of California Los Angeles Loneliness Scales (effect size, 0.14 SD). Although group differences were not statistically significant, the group means for all three variables suggested poorer status in the survivor group. Thus, the pattern of means is consistent with the significant multivariate effect obtained for the social functioning outcome cluster and the significant univariate effect found for the SF-36-SF variable. It is interesting to note that although no group difference emerged on our family functioning measure (ie, MOS-Family Function), significant multivariate and univariate group effects emerged for our dyadic adjustment cluster. Thus, HSCT appears to have the strongest adverse impact on the most intimate of interpersonal relationships—that between the survivor and his or her partner. The impact of HSCT on other social relationships is less clear. Although family functioning did not differ between the survivor and HC groups, these two groups did differ with regard to MOS-Social Function scores.

The HSCT experience also appeared to have a relatively minimal impact on spiritual well-being; the mean effect size for the FACIT-Sp subscale was 0.17. Interestingly, the direction of effect was toward poorer spiritual well-being in the survivor group. Given that the univariate test of differences between the survivor and HC groups for this variable narrowly failed to meet our .05 criterion of statistical significance ($P = .054$), caution in interpreting this finding is warranted. Although enhanced spirituality is often cited as a benefit of the cancer experience, our data did not support this assertion in the HSCT context. Because spirituality and spiritual well-being are difficult concepts to assess, additional investigation of the impact of the HSCT experience in these areas is warranted. Coupled with our finding of poorer dyadic adjustment in HSCT survivors, and contrasted with our finding of greater post-traumatic growth in HSCT survivors, our results suggest growth and enhanced well-being are complex phenomena in the HSCT setting.

Prior research examining HRQOL and other nonmedical outcomes after HSCT suffers from one or more methodologic and conceptual shortcomings, including small, unrepresentative samples; lack of suitable controls; limited length of follow-up; less than comprehensive assessment of HRQOL; and a failure to assess less traditional, yet important outcomes such as growth and spiritual well-being. The methodologic and conceptual strength of our study is evident when judged against this background because our study addresses each of these shortcomings. More specifically, this study includes a large number of HSCT survivors recruited from multiple transplantation centers, used a comprehensive set of outcome indices (including indices of growth and spiritual well-being), and collected data from a matched control group. No prior study of post-HSCT HRQOL indicated this set of significant strengths.

Weaknesses in our study must be acknowledged. The study is cross-sectional and limits our ability to draw inferences about the temporal trajectory of post-HSCT outcomes. In addition, our peer-nomination approach to recruitment of the HC group is not the strongest approach to recruitment of a representative control group. Although we did not use a population-based recruitment strategy (eg, random digit dialing), the sheer magnitude of group differences evidenced suggests our results should not be discounted on this basis alone.

In conclusion, our data clearly indicate disease-free HSCT survivors are, in general, profoundly different from healthy controls. However, the specific manner in which HSCT survivors differ defies easy categorization. Because HSCT survivors evidence deficits across a spectrum of physical, psychological, and social outcomes, it cannot be claimed that HSCT results in a full restoration of health. On the other hand, HSCT survivors evidence improved health in certain respects, specifically those suggestive of growth. Admittedly, our lack of prospective data precludes attribution

of these differences strictly to HSCT. Differences between our survivor and HC groups could have been present before HSCT and might be attributable to the diagnosis and treatment of malignant disease, rather than HSCT, per se. Although possible, we suggest this is largely irrelevant. The critical end result is that HSCT survivors are likely to be profoundly altered, perhaps permanently, by their experience. This has implications for the clinical management of HSCT survivors to achieve optimal restoration of health and functioning.

In addition to justifying continued modification of the HSCT procedure to maximize both disease and HRQOL outcomes, our data suggest supportive care is essential beyond the acute phase of transplantation. Continued monitoring of HRQOL is critical because it can identify deficits in need of remediation. Use of an instrument specifically designed to assess HRQOL rehabilitation needs in the oncology setting, such as the CARES-SF, might be particularly useful in this regard.[62] Furthermore, although psychological, interpersonal, and spiritual growth should never be expected, our data suggest the potential for growth after HSCT is clearly present. Given the traumatic, potentially life-threatening nature of the transplantation experience, the HSCT setting might be an ideal environment for incorporating interventions into routine supportive care that might enhance psychological and interpersonal growth in HSCT survivors. Enhanced growth and benefit-finding have been demonstrated in cancer patients and survivors participating in a variety of interventions, including cognitive-existential group psychotherapy,[63] cognitive-behavioral stress management,[64] and expressive writing.[65] Adaptation of these interventions to the HSCT setting, either in whole or part, to enhance growth and benefit finding in HSCT survivors is likely possible and should serve as a significant goal for future research.

Finally, our results have implications for the pre-HSCT consent process. Most HSCT candidates anticipate a successful transplantation will result in a return to normal, with normal defined as restoration to pre-illness functioning.[66] Failure to meet this expectation has been linked to poorer psychological adjustment in HSCT survivors.[66] Given that a full restoration of health is unlikely in the majority of HSCT recipients, it is critical to communicate this during the pre-HSCT consent process and to continue to reinforce specific information presented during the consent process and encourage realistic expectations for post-HSCT functioning throughout the post-HSCT recovery period. In this regard, informed consent might best be viewed not as a discrete pretransplantation event but as a continuing process that unfolds over time as HSCT recipients recognize and confront new HRQOL concerns during the recovery process.[67]

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Hjermstad MJ, Kaasa S: Quality of life in adult cancer patients treated with bone marrow transplantation—A review of the literature. Eur J Cancer 31A:163-173, 1995
2. Neitzert CS, Ritvo P, Dancey J, et al: The psychosocial impact of bone marrow transplantation: A review of the literature. Bone Marrow Transplant 22:409-422, 1998
3. Wingard JR: Quality of life following bone marrow transplantation. Curr Opin Oncol 10:108-111, 1998
4. Cella DF: Measuring quality of life in palliative care. Semin Oncol 22:73-81, 1995 (suppl 3)
5. Cella D: Quality of life, in Holland JC (ed): Psychooncology. New York, NY, Oxford Press, 1998, pp 1135-1146
6. Andrykowski MA, Brady MJ, Hunt JW: Positive psychosocial adjustment in potential bone marrow transplant recipients: Cancer as a psychosocial transition. Psychooncology 2:261-276, 1993
7. Brennan J: Adjustment to cancer: Coping or personal transition? Psychooncology 10:1-18, 2001
8. Cordova MJ, Andrykowski MA: Responses to cancer diagnosis and treatment: Posttraumatic stress and posttraumatic growth. Semin Clin Neuropsychiatry 8:286-296, 2003
9. Andrykowski MA, Curran SL, Studts JL, et al: Quality of life in women with breast cancer and benign breast problems: A controlled comparison. J Clin Epidemiol 49:827-834, 1996
10. Cordova MJ, Cunningham LLC, Carlson CR, et al: Posttraumatic growth following breast cancer: A controlled comparison study. Health Psychol 20:176-185, 2001
11. Manne S, Ostroff J, Winkel G, et al: Posttraumatic growth after breast cancer: Patient, partner, and couple perspectives. Psychosom Med 66:442-454, 2004
12. Petrie KJ, Buick DL, Weinman J, et al: Positive effects of illness reported by myocardial infarction and breast cancer patients. J Psychosom Res 47:537-543, 1999
13. Sears SR, Stanton AL, Danoff-Burg S: The yellow brick road and the emerald city: Benefit findings, positive reappraisal coping, and positive posttraumatic growth in women with early stage breast cancer. Health Psychol 22:487-497, 2003
14. Tedeschi RG, Calhoun LG: Trauma and Transformation: Growing in the Aftermath of Suffering. Thousand Oaks, CA, Sage, 1995
15. Tedeschi RG, Park CL, Calhoun LG: Posttraumatic Growth: Positive Changes in the Aftermath of Crisis. Mahwah, NJ, Lawrence Earlbaum, 1998
16. Folkman S: Positive psychological states and coping with severe stress. Soc Sci Med 45:1207-1221, 1997
17. Janoff-Bulman R: Shattered Assumptions. New York, NY, The Free Press, 1992
18. Linley PA, Joseph S: Positive change following trauma and adversity: A review. J Trauma Stress 17:11-21, 2004
19. Andrykowski MA, Greiner CB, Altmaier EM, et al: Quality of life following bone marrow transplantation: Findings from a multicentre study. Br J Cancer 71:1322-1329, 1995
20. Bush NE, Donaldson GW, Haberman MH, et al: 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 6:576-591, 2000
21. Chiodi S, Spinelli S, Ravera G, et al: Quality of life in 244 recipients of allogeneic bone marrow transplantation. Br J Haematol 110:614-619, 2000
22. Gruber U, Fegg M, Buchmann M, et al: The long-term psychosocial effects of haematopoietic stem cell transplantation. Eur J Cancer Care (Engl) 12:249-256, 2003
23. Hensel M, Egerer G, Schneeweiss A, et al: Quality of life and rehabilitation in social and professional life after autologous stem cell transplantation. Ann Oncol 13:209-217, 2002
24. Hjermstad MJ, Knobel H, Brinch L, et al: A prospective study of health-related quality of life, fatigue, anxiety, and depression 3-5 years after stem cell transplantation. Bone Marrow Transplant 34:257-266, 2004

25. Kiss TL, Abdolell M, Jamal N, et al: 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 20:2334-2343, 2002

26. 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 19: 1129-1136, 1997

27. Worel N, Biener D, Kalhs P, et al: Long-term outcome and quality of life of patients who are alive and in complete remission more than two years after allogeneic and syngeneic stem cell transplantation. Bone Marrow Transplant 30: 619-626, 2002

28. Hann DM, Jacobsen PB, Martin SC, et al: Fatigue in women treated with bone marrow transplantation: A comparison with women with no history of cancer. Support Care Cancer 5:44-52, 1997

29. Hann DM, Jacobsen PB, Martin SC, et al: Quality of life following bone marrow transplantation for breast cancer: A comparative study. Bone Marrow Transplant 19:257-264, 1997

30. Ware JE Jr, Sherbourne CD: The MOS 36-item short form health survey (SF-36): I. Conceptual framework and item selection. Med Care 30:473-483, 1992

31. Speilberger CD: Manual for the State-Trait Anxiety Inventory. Palo Alto, CA, Consulting Psychologists Press, 1983

32. Radloff LS: The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1:385-401, 1977

33. Weissman MM, Sholomskas D, Pottenger M, et al: Assessing depressive symptoms in five psychiatric populations: A validation study. Am J Epidemiol 106:203-214, 1977

34. Cella DF, Tulsky DS, Gray G, et al: The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. J Clin Oncol 11:570-579, 1993

35. Yellen SB, Cella DF, Webster K, et al: Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) Measurement System. J Pain Symptom Manage 13:63-74, 1997

36. Stewart AL, Ware JE: Measuring functioning and well-being: The Medical Outcomes Study approach. Durham, NC, Duke University Press, 1992

37. Hays RD, Stewart AL: Sleep measures, in Stewart AL, Ware JE (eds): Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Durham, NC, Duke University Press, 1992, pp 235-259

38. Bergner M, Bobbitt RA, Carter WB, et al: The Sickness Impact Profile: Development and final revision of a health status measure. Med Care 19:787-805, 1981

39. Andrykowski MA, Altmaier EM, Barnett RL, et al: Cognitive dysfunction in adult survivors of allogeneic marrow transplantation: Relationship to dose of total body irradiation. Bone Marrow Transplant 6:269-276, 1990

40. Sherbourne CD, Kamberg CJ: Social functioning: Family and marital functioning measures, in Stewart AL, Ware JE (eds), Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Durham, NC, Duke University Press, 1992, pp 182-193

41. Broadhead WE, Gehlbach SH, De Gruy FV, et al: The Duke-UNC functional social support questionnaire: Measurement of social support in family medicine patients. Med Care 26:709-723, 1988

42. Hartshorne TS: Psychometric properties and confirmatory factor analysis of the UCLA loneliness scale. J Pers Assess 61:182-195, 1993

43. Spanier GB: Measuring dyadic adjustment: New scales for assessing the quality of marriage and similar dyads. J Marriage Fam 38:15-28, 1976

44. Langer S, Abrams J, Syrjala K: Caregiver and patient marital satisfaction and affect following hematopoietic stem cell transplantation: A prospective longitudinal investigation. Psychooncology 12:239-253, 2003

45. Northouse LL, Mood D, Templin T, et al: Couples' patterns of adjustment in colon cancer. Soc Sci Med 50:271-284, 2000

46. Tedeschi RG, Calhoun LG: The Posttraumatic Growth Inventory: Measuring the positive legacy of trauma. J Trauma Stress 9:445-471, 1996

47. Peterman AH, Fitchett G, Brady MJ, et al: The Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale (FACIT-Sp). Ann Behav Med 24:49-58, 2002

48. Cella D, Eton DT, Lai J, et al: Combining anchor and distribution-based methods to derive minimally clinically important differences on the Functional Assessment of Cancer Therapy (FACT) Anemia and Fatigue Scales. J Pain Symptom Manage 24:547-561, 2002

49. Hays RD, Wooley JM: The concept of clinically meaningful differences in health-related quality-of-life research: How meaningful is it? Pharmacoeconomics 18:419-423, 2000

50. Norman GR, Sloan JA, Wyrwich KW: Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. Med Care 41:582-592, 2003

51. Flowers MED, Deeg HJ: Delayed complications after hematopoietic cell transplantation, in Blume KG, Forman SJ, Appelbaum FR (eds): Thomas' Hematopoietic Cell Transplantation (ed 3). Malden, MA, Blackwell Publishing, 2003, pp 945-961

52. Sanders JE: Chronic graft-versus-host disease and late effects after hematopoietic stem cell transplantation. Int J Hematol 76:15-28, 2002 (suppl 2)

53. Socie G, Salooja N, Cohen A, et al: Nonmalignant late effects after allogeneic stem cell transplantation. Blood 101:3373-3385, 2003

54. Tabbara IA, Zimmerman K, Morgan C, et al: Allogeneic hematopoietic stem cell transplantation: Complications and results. Arch Intern Med 162:1558-1566, 2002

55. Bhatia S, Louie AD, Bhatia R: Solid cancer after bone marrow transplantation. J Clin Oncol 19:464-471, 2001

56. Kolb HJ, Socie G, Duell T, et al: Malignant neoplasms in long-term survivors of bone marrow transplantation. Ann Intern Med 131:738-744, 1999

57. Socie G, Curtis RE, Deeg HJ, et al: New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. J Clin Oncol 18:348-357, 2000

58. Cohen J: Statistical Power Analysis For the Behavioral Sciences (ed 2). Hillsdale, NJ, Lawrence Earlbaum, 1998

59. Andrykowski MA, Carpenter JS, Greiner CB, et al: Energy level and sleep quality following bone marrow transplantation. Bone Marrow Transplant 20:669-679, 1997

60. Ahles TA, Tope DM, Furstenberg C, et al: Psychologic and neuropsychologic impact of autologous bone marrow transplantation. J Clin Oncol 14:1457-1462, 1996

61. Harder H, Cornelissen JJ, Van Gool AR, et al: Cognitive functioning and quality of life in long-term adult survivors of bone marrow transplantation. Cancer 95:183-192, 2002

62. Hjermstad MJ, Evensen SA, Kvaloy SO, et al: The CARES-SF used for prospective assessment of health-related quality after stem cell transplantation. Psychooncology 12:803-813, 2003

63. Kissane DW, Bloch S, Smith GC, et al: Cognitive-existential group psychotherapy for women with primary breast cancer: A randomized controlled trial. Psychooncology 12:532-546, 2003

64. Antoni MH, Lehman JM, Kilbourn KM, et al: Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early-stage breast cancer. Health Psychol 20:20-32, 2001

65. Stanton AL, Danoff-Burg S, Sworowski LA, et al: Randomized, controlled trial of written emotional expression and benefit finding in breast cancer patients. J Clin Oncol 20:4160-4168, 2002

66. Andrykowski MA, Brady MJ, Greiner CB, et al: "Returning to normal" following bone marrow transplantation: Outcomes, expectations, and informed consent. Bone Marrow Transplant 15:573-581, 1995

67. Andrykowski MA, Cordova MJ, Hann DM, et al: Patients' psychosocial concerns following stem cell transplantation. Bone Marrow Transplant 24:1121-1129, 1999