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Defining Medical Post-traumatic stress AmongYoung Adult Survivors in the Childhood Cancer Survivor Study

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Introduction

Survival of childhood cancer has greatly improved over the past 30 years. However, the decrease in mortality was at the price of increased intensity of treatment, with associated toxicity and resulting morbidity. Many of the treatments were invasive and painful, such as bone marrow biopsies. Repeated hospitalizations separated young children from their parents and all that was familiar. Some of the children and parents experienced the cancer diagnosis and treatment as emotionally traumatic, with responses of horror, intense fear, and/or helplessness and have developed symptoms of Posttraumatic Stress Disorder (PTSD) (1–11).

Response to life-threatening medical illness was included as a potential precipitator for PTSD in the fourth edition of the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association (DSM IV)(12), Since then there have been many studies of the epidemiology of posttraumatic stress responses to childhood cancer (e.g. 3–12), including comparisons of relative risk for PTSD between childhood cancer survivors and

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These data have not been presented previously

Location of work: Childhood Cancer Survivor Study programs (see Appendix)

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their siblings(10). Although most have used a similar conceptualization of posttraumatic stress, variable definitions of PTSD have been employed across studies. Some studies have focused on the number of stress symptoms present (yes/no for each symptom) while others have used symptom severity or frequency (usually based on a Likert scale ranging from 0 to 3 points) (1–2). Studies utilizing gradient measurements permit analyses of factors that contribute to incremental increases of patients' symptoms, whereas studies utilizing dichotomous variables distinguish those whose scores suggest a psychiatric disorder from those whose do not.

Other studies have used the formal diagnostic criteria set by the DSM IV(1), which requires three symptoms of avoidance behavior, two symptoms of increased arousal, and one symptom of re-experiencing the traumatic event, reported more than 30 days after the trauma (3, 8, 10). However, most studies have not included the additional diagnostic requirement of the DSM IV that the symptoms must be severe enough to cause clinically significant distress or functional impairment (10). Some of the studies have created a sub-clinical threshold for a dichotomous variable termed Posttraumatic Stress Symptoms (PTSS), defined as meeting criteria for 2 but not all 3 sets of symptoms (5–9). This variability in definition has made it impossible to compare across studies. It is unlikely that the same predictors of PTSD (e.g. demographic, cancer or treatment characteristics) or the impact of PTSD on later function will result across studies without common criteriain defining PTSD in clinical studies of childhood cancer survivors.

With work currently underway on a fifth edition of the DSM, it is an opportune time to examine the utility of each of the current criteria for Posttraumatic Stress Disorder (PTSD) as applied to cancer survivors. This paper uses data from a large, multi-site epidemiologic study of adult survivors of childhood cancer and their siblings to address the following objectives:

1. To examine the prevalence of PTSD in childhood cancer survivors and siblings using different operational definitions of PTSD
2. To examine the associations between these different operational definitions of PTSD and commonly examined demographic and medical variables
3. To determine the relative predictive ability of the total number of posttraumatic stress symptoms and the severity oftotal symptoms in the prediction of functional impairment and/or clinically significant distress of childhood cancer survivors

Methods

Sample

The Childhood Cancer Survivor Study (CCSS) is a longitudinal cohort study that tracks the health status of survivors of childhood cancer diagnosed between 1970 and 1986 and treated at collaborating centers across the United States and Canada. The institutional review board at each collaborating center reviewed and approved the CCSS protocol and documents sent to participants. All study participants provided informed consent for participation in the study and for medical-record abstraction. Detailed descriptions of the study design and characteristics of the cohort have been reported in previous papers (13–15).

Of the 20,691 long-term survivors of childhood cancer identified for the original cohort, 3,058 (14.8%) were lost to follow-up despite extensive efforts to locate them. Among the remaining 17,633 survivors, 14,358 (81.4%) completed the baseline questionnaire. In addition, a sample of the participating survivor population were randomly selected and asked to nominate their nearest age sibling to be a part of the comparison group. Of the

6,100 siblings nominated, 4,870 were deemed willing and eligible, and 4,023 (82.6%) participated in the baseline survey. Beginning in 2003, 11,576 (80.6%) of the original survivor cohort were contacted and requested to participate in a follow-up survey that focused on psychosocial outcomes. Of these, 9,308 (80.4%) survivors completed and returned a survey, 6,542 (70.3%) of whom were over 18 years of age and had completed all survey items required for this study without use of a proxy reporter. A sub-sample of 500 of the original siblings who were over age 18 was randomly selected to complete the 2003 follow-up survey that contained psychosocial assessment items. Of these, 374 (74.8%) completed all of the items of interest to this study. The descriptive statistics for the demographic and medical variables of the survivors and siblings have been previously published (10).

Measures

The symptoms of PTSD were assessed using the Posttraumatic Stress Diagnostic Scale (PDS) (16). This measure includes 17 questions based on diagnostic symptomcriteria for PTSD in the DSM IV (12), rated on a 0 to 3 scale for frequency of occurrence (severity of symptoms) in the past month (0=“Not at all or only one time”, 1=”Once in a while”, 2= “Half the time”, and 3= “Almost always”). Symptoms rated at 1 or above were counted as present.

The PDS measure can be used as a continuous measure of posttraumatic stress symptoms or as a dichotomous scale. This measure and threshold for dichotomous coding has demonstrated good internal consistency andtest-retest reliability, as well as satisfactory convergentand concurrent validity in past studies when compared with clinical diagnoses of PTSD based on a standardized diagnostic interview (17).For this study the PDS symptoms were used in three ways (defined in Table 1):

1) Criteria for DSM symptom clusters

2) Number of the 17 symptoms endorsed

3) Severity /frequency of symptoms

Performance on the Brief Symptom inventory (BSI-18) and the RAND Health Status Survey Short Form 36 (SF-36) were used to determine whether survivors met criterion F of the diagnostic criteria for PTSD in the DSM IV (12).The Brief Symptom Inventory-18 (BSI-18) is an 18 item self-report questionnaire which evaluates current psychological distress using a summary scale, the global stress index (GSI), and three subscales: depression, anxiety, and somatization (18). The items are rated on a 5 point scale, with distress ratings ranging from 0 (not at all) to 4 (extremely). Age and gender-corrected T-scores are used, based on adult non-patient community norms (mean = 50, standard deviation = 10). Clinically significant distress is defined as a T-score greater than or equal to 63on the GSI or on any two of the three subscales, representing a level of distress that falls above the 90^{th} percentile of the normative sample. The BSI-18 has been validated with healthy volunteers (18) as well as with earlier surveys of this cohort of cancer survivors (19, 20), and has been widely used in a variety of other clinic research samples. Those survivors with either a T-score ≥ 63 on the BSI-18 GSI score or on two of the BSI subscales (i.e. depression, anxiety, or somatization), were determined to meet criterion F based on clinically significant distress.

The RAND Health Status Survey, Short Form-36 (SF-36) is a 36 item self-report measure used to assess functional impairment (21). Scales generated include physical functioning; bodily pain; role limitations due to physical health problems; role limitations due to emotional health; general mental health; social functioning; energy/fatigue; and general health perception. Norm-referenced T scores are used (mean= 50, standard deviation = 10), with functional impairment defined as scores ≤ 40, representing a level of functioning that

falls below the 16th percentile of the normative sample. The RAND SF-36 has received extensive reliability and validity testing (22), and has demonstrated sensitivity in the CCSS cohort (23).Those survivors who obtained a T-score ≤ 40 on the role limitations due to emotional health scale on the SF-36 were determined to meet criterion F based on functional limitations.

Analyses

The first objective of these analyses was to examine the prevalence of PTSD in survivors and siblings using different operational definitions of PTSD. Participants were grouped into one of five mutually exclusive categories:

Group 1 Survivors or siblings who reported the DSM IV diagnostic requirements of at least 1 re-experiencing symptom, 2 arousal symptoms and 3 avoidance symptoms (Full PTS symptoms), ANDmet BSI criteria for significant distress or the SF36 criteria for functional impairment (F criteria).

Group 2 Survivors or siblings who reported the DSM IV diagnostic requirements (Full PTS symptoms)AND DID NOT meet F Criteria.

Group 3Survivorsor siblings who reported symptoms consistent with the requirements for 2 but not all 3 of the symptom clusters(Partial PTS symptoms) ANDmet F criteria

Group 4 Survivorsor siblings who reported Partial PTS symptoms AND DID NOT meet the F criteria

Group 5 All other survivors and siblings (less than two clusters of symptoms)

Four operational definitions of PTSD were generated, based on dichotomous outcomes corresponding to the first four groups above. Prevalence of PTSD using these different definitions was compared between survivors and siblings using odds ratios (ORs) and p-values evaluated from logistic regression with robust variance estimates to account for intra-family correlation.

The second objective of the analyses was to examine the associations between different definitions of PTSD and survivors' demographic and medical variables. For this analysis the groups above were treated as an ordinal outcome, and aproportional odds model was fit, utilizing cumulative logits for the binary outcomes defined as follows:Group 1 versus 2,3,4,5; Groups 1 and 2 versus 3, 4,5; Groups 1, 2 and 3 versus 4, 5; Groups 1, 2, 3, and 4 versus 5. Under a standard proportional odds model, a common odds ratio across these binary cutpoints is assumed for each factor in the model, providing evidence that defining PTSD based on any of the above operational definitions results in similar associations with covariates. The proportional odds assumption was violated for some covariates, so a partial proportional odds model was fit, allowing impact of those factors to vary across cutpoints (24), providing evidence, for those factors, of different associations depending on the PTSD definition utilized. Due to significant interactions, some covariates were stratified on age at diagnosis. Modeling was conducted using SAS version 9.1 (25).

The third objective of the analyses was to determine the relative power of the total number of posttraumatic stress symptoms, and the severity/frequency oftotal symptoms to predict survivors' functional impairment and/or clinically significant distress. To assess this, we employed receiver operating characteristic (ROC) curves, a two-dimensional summary of sensitivity and specificity for a marker. The ROC curve illustrates the trade-off in true positive vs. false positive rates for a specific outcomeover the full range of potential thresholds for a continuous marker (26). In this case, the markers under evaluation were number and severity/frequency of symptoms, with impairment and distress used as

outcomes to be predicted. The BSI-18 and the SF-36 were used to define those who had functional impairment and/or clinically significant distress.

To compare severity and number of symptoms as predictors, ROC curves were constructed for each, with either impairment or distress as the outcome. Since the interest in this study was in correctly identifying those with impairment or distress, we computed the associated false positive rates at true positive rates of 70%, 80%, and 90%, along with the associated cutpoints for the markers. ROC estimation was conducted using R version 2.11.0 (27).

Results

Definitions of PTSD:Full versus Partial Symptoms with or without Impairment

Table 2 presents the prevalence of posttraumatic stress according to the definitions of each Group for both siblings and survivors. As would be expected, the prevalence within survivors and siblings varied with different operational definitions. Compared to siblings, survivors demonstrated significantly higher rates of posttraumatic stress when defined as meeting full symptoms plus functional impairment (OR 4.21, 95% CI 2.11–8.38), and when meeting either full (OR 2.85, 95% CI 1.51–5.39) or partial (OR 1.71, 95% CI 1.13–2.60) symptoms without impairment, but not partial symptoms plus functional impairment (OR 1.42, 95% CI 0.79–2.56).

Within the survivor sample, group membership was associated with demographic and illness-related variables. For most variables the proportional odds assumption was met, demonstrating a consistent association when moving between each level of Group definition. As such, multivariable odds ratios are presented for the common odds ratio (Table 3). Females were 19% more likely than males to demonstrate significant symptoms of PTSD across all definitions (OR 1.19, 95% CI 1.05–1.34). In separate modeling, intensity of cancer therapy, dichotomized as yes/no based on type and/or duration of chemotherapy, surgery, and radiation therapy (10) was also a notable predictor of number of PTSD symptoms and associated impairment (common OR 1.56, 95% CI 1.34–1.81, not shown in table).

In contrast to the consistent effect of variables across definitions as outlined in Table 3, marital status and employment demonstrated non-proportional impactson the PTSS outcome (caseness), depending on the number of symptoms and impairment used for the definition (Table 4). Survivors who are single hada 90% increased rate of having full symptoms plus impairment (Group1) compared to those who were married (OR 1.90, 95% CI 1.54–2.33). However, if the definition is changed to include any number of symptoms of PTSD with or without impairment (Groups 1, 2, 3, and 4) versus no significant symptoms (Group 5), theodds associated with being single are only 44% higher compared to those who are married (OR 1.44, 95% CI 1.26–1.65). Similar findings can be seen for employment, where survivors who were unemployed had a two-fold increased rate of full PTSD symptoms with impairment (i.e. Group 1) compared to survivors who were employed (OR 2.06, 95% CI 1.68–2.53). By expanding the definition to include any symptoms of PTSD with or without impairment (i.e. Groups 1, 2, 3, or 4), the increased risk associated with unemployment is only 41% (OR 1.41, 95% CI 1.22–1.63).

Number of symptoms or severity as a marker for impairment and/or distress

Using the area under the curve (AUC), both severity/frequency of symptoms and number of symptoms were shown to be significantly better (p-value<.0001) at discriminating between those with and without emotional distress than between those with and without functional impairment, (AUCs =0.84 and 0.82 versus 0.74 and 0.74, respectively). There is no significant difference between using the total number of symptoms or the severity/frequency

of symptoms in the accurate prediction of functional impairment or emotional distress. Table 5 presents the false positive rates when true positive rates are set for 70%, 80% and 90% for the BSI (distress) and the SF-36 (functional impairment). A threshold of 6 for severity of symptoms will correctly identify 80% of survivors with emotional distress, but incorrectly identify 27% as having emotional distress.

DISCUSSION

These results raise interesting questions about what operational definitions of PTSD is best used in studies of childhood cancer survivors. Different operational definitions made significant differences not only in prevalence of PTSD in childhood cancer survivors, but also in the difference between prevalence in survivors compared to healthy siblings. The odds ratio is much greater between survivors and siblings for full symptoms plus distress/impairment (4.21) and partial symptoms plus distress/impairment (2.85) than for either definition which did not include distress or impairment (1.71 and 1.42).The various operational definitions also differed in their relationship to demographic and illness-related variables. The greater number of women than men was consistent across all definitions of PTSD, and is consistent with previous studies with other trauma groups (28, 29). However, other variables such as employment and marital status appear to be differentially related, depending on the operational definition used for PTSD. It may be that variables like education and marriage have thresholds for disruption which may not be breached until severe levels of PTSD symptoms and impairment are obtained (10). Studies examining potential predictors or risk factors for PTSD in childhood cancer survivors will likely find different results depending on the threshold they use for defining medical PTSD. This finding has not been previously published, and has important implications for future studies.

There does not seem to be a significant difference between use of number or of severity/frequency of symptoms in predicting clinical distress or functional impairment. The findings support the current use of a low threshold (1 on a 0 to 3 scale) to define a symptom as “present” for commonly used tools (17, 30). It appears that the presence of a symptom even as seldom as once a week in the past month is enough to be clinically significant, if there are enough different symptoms.

Both number and severity/frequency of PTSD symptoms are significantly better at predicting clinical distress than functional impairment. Although functional impairment in this study was evaluated using the role limitations due to emotional health scale of the SF-36, it appears that the specific symptoms of posttraumatic stress are more closely associated with active symptoms of depression, anxiety and somatization (as measured by the BSI) than with role limitations. This is not particularly surprising, as many of the symptoms of PTSD overlap symptoms of anxiety or depression.

There are a number of limitations to this study. First is that all of the survivors experienced the trauma of the life-threatening illness as children. There is some evidence that repeated traumatic events during childhood have a different long-term impact than similar events occurring during adulthood (32). It may be that these findings are specific to adult survivors of cancer diagnosis and treatment during childhood, and would not generalize to subjects experiencing cancer diagnosis and treatmentas adults. It is also not clear how much these findings apply to other types of medical trauma. Another limitation is that the siblings are really a comparison rather than a control group, as they were also exposed to a potentially traumatic event, the serious illness of a family member. More research will be needed to clarify whether or not cancer or other medically traumatic events have essentially the same impact or are substantially different from other types of traumatic events, whether during childhood or for adults.

A common limitation of such a large study is that the data are all from self-report surveys, and participants are self-selected from a larger initial group. There is always some concern that those who responded over- or under-estimated their symptoms, and that those with more severe symptoms chose not to participate. This was examined in a previous study (10) and there does not appear to be an obvious difference on the variables associated with full PTSD, but this may be different for the other threshold levels.

Despite these limitations, the results of the current investigation offer valuable data for consideration of classification and diagnostic guidelines. On the basis of these findings, we suggest that the DSMV:

- Continue to include medical trauma as a potential precipitant for PTSD.
- Retain the requirements for clinically significant distress and or functional impairment for PTSD, even if not used universally throughout the DSM V.
- Use presence, and not severity, of symptoms for diagnosis.

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Table 1

Definitions of variables

Variable name	Definition
Criteria for symptom clusters	3 symptoms of avoidance behavior, 2 symptoms of increased arousal, and 1 symptom of re-experiencing
Number of symptoms endorsed	A symptom was counted if endorsed 'Once in a while' or greater. The results for all 17 symptoms were summed, generating a score ranging from 0 to 17.
Severity /frequency of symptoms	Severity/frequency of symptoms was evaluated using the weighted response for each symptom (0 to 3 point scale). The results were summed, generating a score of 0 to 51.

Table 2

Prevalence of posttraumatic stress symptoms by Group

Post-traumatic stress: symptomatic groups		Sibling		Survivor		Odds ratio (95% C.I.)	P-value
		N	%	N	%		
Full symptoms, impairment or distress	No	366	97.9	5953	91.0	4.21 (2.11 –8.38)	<.0001
	Yes	8	2.1	589	9.0	1.0	
Full symptoms, no impairment or distress	No	364	97.3	6052	92.5	2.85 (1.51 –5.39)	0.0013
	Yes	10	2.7	490	7.5	1.0	
Partial symptoms (2 of 3), impairment or distress	No	362	96.8	6228	95.2	1.42 (0.79 –2.56)	0.24
	Yes	12	3.2	314	4.8	1.0	
Partial symptoms (2 of 3), no impairment or distress	No	344	92.0	5798	88.6	1.71 (1.13 –2.60)	0.012
	Yes	30	8.0	744	11.4	1.0	

Table 3

Relationship of symptomatic groups to treatment, demographic and personal informationResults from multivariable partial proportional odds model with ordinal symptomatic group outcome. Covariates with proportional odds, in the same model as in Table 4.

Covariate	Level	Common odds ratio and 95% C.I.
Gender	Male	1.0
	Female	1.19 (1.05 – 1.34)*
Race	White non-Hispanic	1.0
	Other race	1.10 (0.93 – 1.30)
Age at interview	18–29	1.0
	30–39	1.15 (0.97 – 1.36)
	40+	1.03 (0.81 – 1.30)
Age at dx 0–4: Education	College graduate	1.0
	High school	1.55 (1.19 – 2.03)*
	Some college	1.01 (0.81 – 1.25)
Age at dx 5–9: Education	College graduate	1.0
	High school	1.12 (0.79 – 1.57)
	Some college	1.04 (0.81 – 1.35)
Age at dx 10–14: Education	College graduate	1.0
	High school	1.01 (0.70 – 1.47)
	Some college	1.61 (1.25 – 2.07)*
Age at dx 15–20: Education	College graduate	1.0
	High school	1.05 (0.70 – 1.58)
	Some college	1.17 (0.89 – 1.54)
Chemotherapy	None	1.0
	Anthracycline/alkylating	1.25 (1.08 – 1.45)*
	Other chemo	1.34 (1.11 – 1.62)*
Age at dx 0–4: Radiation	None	1.0
	CRT	2.10 (1.68 – 2.63)**
	Other RT	1.42 (1.11 – 1.82)*
Age at dx 5–9: Radiation	None	1.0
	CRT	1.12 (0.85 – 1.49)
	Other RT	1.29 (0.95 – 1.74)
Age at dx 10–14: Radiation	None	1.0
	CRT	0.92 (0.69 – 1.24)
	Other RT	1.07 (0.81 – 1.41)
Age at dx 15–20: Radiation	None	1.0
	CRT	0.88 (0.60 – 1.29)
	Other RT	0.92 (0.69 – 1.22)

Covariate	Level	Common odds ratio and 95% C.I.
Personal Income	$40K+	1.0
	<$20,000	1.41 (1.19 – 1.67)**
	$20K–$39K	1.05 (0.90 – 1.24)
Recurrence	No	1.0
	Yes	1.29 (1.08 – 1.54)*
SMN	No	1.0
	Yes	1.21 (1.00 – 1.46)

Model adjusted for all variables shown above.

P-values:

* <.01,

** <.001

Table 4

Relationship of symptomatic groups to treatment, demographic and personal informationResults from multivariable partial proportional odds model with ordinal symptomatic group outcome. Covariates with nonproportional odds, all in the same model, adjusted for all variables shown above.

		Odds ratio and 95% C.I. with p-value			
Covariate	**Level**	**Group 1 vs. 2–5**	**Groups 1–2 vs. 3–5**	**Groups 1–3 vs. 4–5**	**Groups 1–4 vs. 5**
Employed	Yes	1.0	1.0	1.0	1.0
	No	2.06 (1.68 – 2.53)*	1.38 (1.16 – 1.64)*	1.55 (1.32 – 1.81)*	1.41 (1.22 – 1.63)*
Marital status	Married/living as married	1.0	1.0	1.0	1.0
	Single	1.90 (1.54 – 2.33)*	1.47 (1.24 – 1.73)*	1.54 (1.32 – 1.79)*	1.44 (1.26 – 1.65)*
	Widowed/divorced/separated	2.29 (1.68 – 3.12)*	1.60 (1.23 – 2.07)*	1.60 (1.26 – 2.03)*	1.57 (1.26 – 1.94)*

P-values:

* <.01,

** <.001

Table 5

Statistics for severity and number of PTSD symptoms as markersof clinical distress and functional impairment

BSI (significant distress)							
Marker	**AUC**	**TPR of 70%**		**TPR of 80%**		**TPR of 90%**	
		Threshold	**FPR (95% CI)**	**Threshold**	**FPR (95% CI)**	**Threshold**	**FPR (95% CI)**
Severity of symptoms	0.84 (0.82, 0.85)	10	14% (12%, 20%)	6	27% (23%, 33%)	2	54% (45%, 65%)
Number of symptoms	0.82 (0.80, 0.84)	6	21% (15%, 22%)	4	33% (26%, 41%)	1	63% (50%, 64%)

SF-36 mental summary (functional impairment)							
Marker	**AUC**	**TPR of 70%**		**TPR of 80%**		**TPR of 90%**	
		Threshold	**FPR (95% CI)**	**Threshold**	**FPR (95% CI)**	**Threshold**	**FPR (95% CI)**
Severity of symptoms	0.74 (0.73, 0.76)	5	30% (29%, 37%)	2	52% (43%, 53%)	0	84% (83%, 85%)
Number of symptoms	0.74 (0.72, 0.75)	4	31% (30%, 40%)	2	49% (48%, 61%)	0	84% (83%, 85%)

AUC=Area under the curve; TPR = True Positive Rate; FPR = False Positive Rate