

Posttraumatic stress-related psychological functioning in adult survivors of childhood cancer

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Abstract

Purpose The majority of research examining posttraumatic stress symptoms/disorder (PTSS/PTSD) among adult survivors of childhood cancer has been oriented to cancer, assuming that cancer has been the most traumatic experience in their lives. Whether that assumption is valid, and how it might impact assessment of PTSS, is unknown.

Methods Survivors in the St. Jude Lifetime Cohort study completed an assessment of PTSS without cancer orientation, global psychological functioning, perceived stress, and cancer-related anxiety.

Results Participants ($n = 2969$; $M_{\text{age}} = 32.5 \pm 8.5$ years, 24.1 years since diagnosis, 49.1% female) obtained a mean score on the PTSD Checklist of 27.7, which is comparable to a normative population. Using established cutoffs, 11.8% obtained scores in the at-risk range. Multivariable modeling indicated that psychological factors [global distress ($p < 0.0001$), perceived stress ($p = 0.001$), cancer-related anxiety ($p < 0.0001$)] and demographic variables [female gender ($p < 0.0001$), survivors with less than a college education ($p = 0.002$)] were risk factors for increased PTSS. Only 14.5% identified a cancer-related traumatic event, and there

was no difference in PTSS scores between those who identified cancer vs. non-cancer events as most stressful (28.4 ± 12.6 vs. 28.5 ± 12.7 , $p = 0.93$).

Conclusion One in eight adult long-term survivors of childhood cancer had PTSS above the cutoff, though subgroups (e.g., females and those with lower education) report more distress symptoms. Most adult survivors do not identify cancer as their most stressful event.

Implications for cancer survivors Screening for distress in survivorship clinics should not assume that distress is directly related to the survivor's cancer experience.

Keywords Posttraumatic stress · Cancer survivorship · Adult survivors · St. Jude Lifetime Cohort (SJLIFE)

Introduction

The 5-year survival rate for childhood cancer now exceeds 84%, primarily due to advancements in treatment and participation in clinical trials [1]. Survivors are commonly described as resilient, and even those who experience emotional distress often report psychological growth as a result of their cancer experience [2]. Among long-term survivors of childhood cancer, certain factors have been reported to heighten levels of emotional distress, such as cancer-related pain, learning, and memory problems [3], and health perceptions including fears related to fertility, overall health, and mortality [4]. While those survivors who experience distress are in the minority, research has focused on describing the prevalence and associated risk factors for adverse psychological outcomes.

The construct of posttraumatic stress symptoms and disorder (PTSS/PTSD) has frequently been used as a means of understanding psychological distress among survivors [5, 6], particularly with the addition of a life-threatening medical

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illness as a qualifying event for PTSD in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision* (DSM-IV) [7, 8]. PTSS, or sub-clinical levels of symptoms related to PTSD, is one of the most frequently studied psychological constructs in youth with cancer, with overall prevalence rates varying widely [9–11]. Rates in long-term survivors are also variable, with some studies demonstrating significantly higher rates of PTSD among survivors compared to sibling controls [12], and others [13] demonstrating that long-term survivors report fewer PTSS than those who are closer to diagnosis, as well as peer comparisons without a history of cancer. A variety of fixed (e.g., female sex, lower educational level, being unemployed), modifiable (e.g., poor family functioning, perceived severity of cancer diagnosis/treatment intensity, lack of family/social support), and relational (e.g., exposure to PTSD in the home, having a parent with PTSD) risk factors have been identified [11].

Differences in methodology of assessment, including orientation to cancer and lack of control groups have been proposed as a reason for the reported variability in prevalence rates of PTSS/PTSD in survivors [13]. There are two primary methods that have been used to assess PTSS/PTSD in survivors of childhood cancer. In the first, survivors are asked to rate the presence of PTSS/PTSD when they think about cancer. In this way, cancer is presumed to be their most traumatic event. Some [13] have argued that this leads to a “focusing” effect that may arbitrarily increase the presence of symptoms. The second approach used by researchers allows respondents to spontaneously identify their most stressful event, without presuming that they will choose cancer. This potentially allows for more accurate identification of survivors with PTSS/PTSD who identify cancer as their most traumatic experience compared to those with PTSS/PTSD who identify a non-cancer-related traumatic event. It also allows for an identical assessment approach in a healthy comparison sample. It should be noted that in studies that have assessed PTSS/PTSD without orientation to cancer, only 10–20% of long-term survivors have identified a cancer-related event as their most traumatic [13, 14].

The gold standard for the diagnosis of PTSD is a semi-structured diagnostic interview such as the Clinician-Administered PTSD Scale (CAPS) [15]. However, given the time-intensive nature of this methodology, it is underutilized in research settings. As a more efficient alternative, most studies rely on questionnaire measures, with respondents asked to answer questions that assess the primary symptoms of PTSD in relation to a specific event (of their choosing or one that is provided for them). However, it has been suggested that a better alternative is the use of a screening questionnaire regarding the presence of symptoms—in general, not in the context of an event—followed by a diagnostic interview such as the CAPS [16]. This interview would then be used to identify a traumatic event, determine whether it met DSM criteria, and assess the presence of symptomatology as a result of that

event. For example, the PTSD Checklist (PCL) was designed as such a screening instrument, rather than for diagnostic clarification [17]. Therefore, if the PCL revealed significant levels of distress, a more formal diagnostic interview would be warranted in order to assess whether a diagnosis of PTSD is applicable. This is not a methodology that has yet been used with adult survivors of childhood cancer.

Further work is needed to identify the extent to which long-term survivors are experiencing PTSS/PTSD, without the presumption that cancer is a traumatic experience for all survivors. If survivors do report significant distress, it is important to understand the factors that may influence their level of distress so as to aid prevention/intervention efforts. As such, the objectives of this study are to evaluate the presence of PTSS among long-term survivors—without assuming cancer as the traumatic event—and to identify biological, psychological, and social factors that may be associated with PTSS in survivors. A large, heterogeneous sample of 10+-year adult survivors of childhood cancer was assessed. We hypothesized that the proportion of survivors endorsing clinically significant levels of PTSS would not be higher than the expected prevalence rates for civilians. Furthermore, we anticipated that the majority of participants would identify a non-cancer-related traumatic event, hypothesizing that no significant differences in rates of PTSS would be present among those who identify cancer vs. a non-cancer-related traumatic event. Finally, we hypothesized that while overall, survivors will report low mean levels of psychological distress, higher rates of PTSS would be observed for those who are female, unemployed, and have lower educational attainment.

Methods

Participants

Eligible participants were enrolled in the St. Jude Lifetime Cohort (SJLIFE) study, which is a longitudinal epidemiological study of long-term survivors of childhood cancer who were treated at St. Jude Children’s Research Hospital (SJCRH) [18, 19]. Eligibility criteria for SJLIFE include the following: (1) diagnosis of malignant disease and treated at SJCRH, (2) at least 10 years from diagnosis, and (3) age 18 or older at study entry. During the recruitment period, eligible survivors are offered different levels of participation, including (1) comprehensive evaluation completed at SJCRH or (2) completion of a structured survey. Recruitment is ongoing; however, as of June 30, 2014, 4566 survivors of childhood cancer were potentially eligible for SJLIFE. To be included in the current project, survivors had to have completed the PTSD Checklist-Civilian Version [17]. A total of 4566 survivors were confirmed eligible, among which 3010 participated. After further review, 121 were inevaluable because they did not complete the PTSD Checklist-

Civilian (PCL-C) Version; therefore, 2969 (65.0%) were evaluable for the current project (Fig. 1).

Assessment measures

Posttraumatic stress symptoms *PCL-C* [17] is a 17-item screening tool that reflects the DSM-IV symptoms of PTSD in relation to general “stressful experiences” and is applicable with any population. Respondents are instructed to answer the items based on how much they were bothered by the identified symptom in the past month. Answers are given on a Likert scale ranging from “not at all” to “extremely.” Scores ≥ 44 indicate a positive screen for civilians [20], and this was used in the current study; Cronbach’s alpha for the current sample was 0.94. After completion of the PCL-C, participants were asked to write down the most difficult or stressful event they had ever experienced. These events were subsequently categorized as cancer or non-cancer-related.

Perceived stress *Perceived Stress Scale* (PSS) [21] is a measure of the extent to which an individual appraises situations in one’s life to be stressful, and the degree to which one’s life is believed to be unpredictable, uncontrollable, and overloading. The short form (4-items) was used in the current project. Answers are provided based on a 5-point Likert scale from “never” to “very often” and respondents are instructed to endorse their responses based on how often they felt a certain way in the past month (Cronbach’s alpha = 0.74). For purposes of the current project, a total score was used in analyses, with higher scores indicative of greater perceived stress.

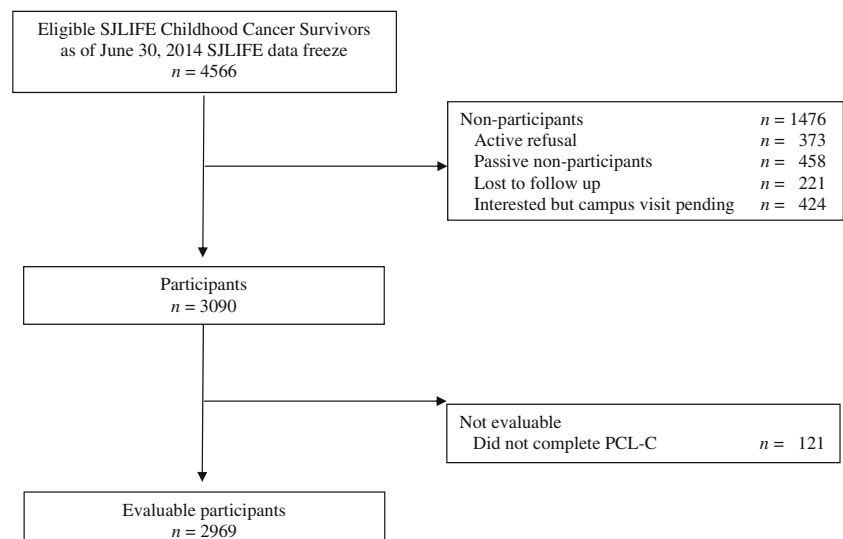
Psychological functioning *Brief Symptoms Inventory-18* [22] is an 18-item measure that evaluates psychological distress. It has been validated with adult survivors of childhood cancer

[23]. Respondents answer questions using a 5-point Likert scale ranging from “not at all” to “extremely” based on the frequency of their symptoms over the past 7 days. Scores are transformed into standardized T-scores (mean = 50, SD = 10); the Global Symptoms Index (GSI) was used for analyses (Cronbach’s alpha = 0.92). *Worry questions* (5 items) were developed for the SJLIFE study [24, 25] and a 5-point Likert scale ranging from “strongly disagree” to “strongly agree” was used to assess participants’ concerns about their cancer. Questions assess general fears about cancer, concerns about physical problems and appearance in relation to cancer, fear of relapse, and worry prior to checkups. A total score was used for analyses, with higher scores indicative of greater worry (Cronbach’s alpha = 0.81).

Statistical analyses

Descriptive statistics were generated to characterize the demographic and treatment characteristics of the study population. Multiple linear regression was used to assess the effects of various demographic, treatment, and psychological predictors on the total stress score from PCL-C. Diagnostic group (leukemia/lymphoma, central nervous system (CNS), other diagnoses), age at diagnosis, and gender were forced in the model a priori. Other factors for selection included demographic factors such as age, race, marital status, employment, living arrangements, education, and household income, diagnosis of a second cancer, and psychological functioning (BSI GSI T-score, PSS total score, and Worry Scale total score). The selection of variables to be included in the final model was done using a Bayesian model averaging (BMA) [26] approach. BMA model selection was conducted in R (Vienna, Austria); all other analyses were completed in SAS v9.3 (Cary, NC).

Fig. 1 CONSORT diagram



Results

Descriptive analyses

Survivors were, on average, 32.5 years old and 24.1 years from diagnosis at survey completion. Participants were approximately 8.4 years old when they were diagnosed. The sample was evenly split between female (49.1%) and male participants and the majority of the sample was Caucasian (85.0%), married (50.2%), and living with their spouse (51.0%). The majority (65.3%) earned less than a college degree, were employed full-time (58.8%), and grossed more than \$40,000 per year (54.9%). Cancer diagnostic categories were varied and primarily comprised of leukemia/lymphoma (57.9%), solid tumors (31.7%), and CNS tumors (9.9%). Most survivors were treated with radiation (60.1%) and/or chemotherapy (85.8%). Fewer received bone marrow transplant (4.3%), had disease relapse (11.2%), or developed a second cancer (15.2%). Survivor descriptives are presented in Table 1. Of note, analyses were completed to assess potential differences between participants and non-participants. Participants were approximately 1.9 years older ($p < 0.001$) and more likely to be female (< 0.001) than non-participants. However, there were no differences in age at diagnosis or diagnostic category.

Provided in Table 2 are the descriptive statistics for the assessment measures. The mean score for the PTSD Checklist ($M = 27.7$; $SD = 12.4$) is well below the at-risk cutoff (≥ 44) [16]. Approximately 11.8% of survivors had PCL-C scores above the cutoff. These survivors (56.2% female) were on average 34.2 years old ($SD = 7.8$) at the time of assessment and 25.0 years from their diagnosis ($SD = 8.3$). With regard to diagnosis, 63.3% were diagnosed with leukemia/lymphoma, 4.9% with a CNS tumor, and 31.8% with other cancer diagnoses. Additionally, 11.5% had experienced relapse and 18.9% had been diagnosed with a second malignancy.

Mean scores on the GSI from the BSI were very similar to established norms ($M = 50.0$; $SD = 11.3$), with 15.6% of exceeding the cutoff for clinically significant levels of psychological distress. Responses on the cancer-related worry questions had a mean equivalent to a “neutral” response ($M = 14.4$; $SD = 4.8$).

Modeling: correlates of PTSS

The total score of the PCL-C was significantly associated with gender (female; estimate = 1.64), education (less than college; estimate = 0.90), and diagnostic category (CNS tumor; estimate = - 1.15). Specifically, females were more likely than males to report increased levels of distress, as were survivors with less than a college education in comparison to survivors with at least some college education. Survivors of leukemia/

lymphoma reported slightly more distress (estimate = 0.12, non-significant) than survivors of other tumors, while survivors of CNS tumors reported significantly less distress (estimate = - 1.15). There was no association for age at diagnosis. As expected, higher PSS (estimate = 0.76), GSI (estimate = 0.67), and cancer-related worry (estimate = 0.10) scores were significantly related to increased reports of stress-related distress. Modeling results are presented in Table 3.

Exploratory analyses: stressful event identification

When asked to provide a traumatic or stressful event, 35.5% of participants did not identify a specific event. Among those who did report an event, 85.4% reported a non-cancer-related traumatic event and 14.6% identified cancer as a traumatic event. No significant difference was found between those who identified cancer as a traumatic event ($M = 28.4$, $SD = 12.6$) or a non-cancer event ($M = 28.5$, $SD = 12.7$) in regard to overall level of PTSS on the PCL-C ($p = 0.93$). However, those who did not report any traumatic event ($M = 26.4$, $SD = 11.7$) had significantly lower total PCL-C scores than those who reported a cancer ($p < 0.001$) or a non-cancer ($p = 0.01$) event.

Discussion

In this large population of very long-term survivors of childhood cancer, measures of psychological distress and posttraumatic stress were found to be in the average range, and comparable to normative samples. Likewise, the percentage of survivors meeting or exceeding established cutoffs for at-risk status was in the expected range, with about 12% screening positive [16]. However, it is important to consider that the PCL-C is a screening tool; as such, these results only suggest that these individuals would benefit from a diagnostic interview to formally assess for PTSD symptomatology, not that they meet the diagnostic criteria for PTSD. If diagnostic interviews were conducted with those survivors who screened positive, it is not expected that all would meet the criteria for PTSD, but that rates of those meeting criteria would be similar to the 6.8% overall lifetime rates for a civilian population (9.7% in women, 3.6% in men) [27, 28]. For example, a meta-analysis of PTSD among individuals with breast cancer revealed significant differences between prevalence rates of PTSD based on self-report instruments (11.4%) and clinical interview (5.6%) [29]. These differences are even more striking in military settings. For example, in a study of Iraqi war veterans, 21% screened positive for PTSD using survey questionnaires, which declined to 4% when based on diagnostic interview [30]. From that perspective, it appears that the rate of PTSD in our survivor sample may not be higher than that in

Table 1 Demographic and cancer-related characteristics of study participants (*N* = 2969)

Demographic characteristics	<i>N</i> (%)
Age (years)	
Mean ± SD	32.5 ± 8.5
Median	31.5
Range	18.3–63.8
Gender	
Female	1457 (49.1)
Male	1512 (50.9)
Race	
White	2525 (85.1)
African American	402 (13.5)
Other	42 (1.4)
Marital status	
Single, never married	1071 (36.1)
Married, living as married	1489 (50.2)
Separated, divorced, widowed	405 (13.7)
Living arrangements	
Living with spouse	1511 (51.0)
Living with others (siblings, parents, roommates)	1074 (36.3)
Living alone	375 (12.7)
Employment status	
Full time	1736 (58.8)
Part time	374 (12.7)
Unemployed	840 (28.5)
Education	
Some college or less	1904 (65.3)
College graduate or more	1014 (34.7)
Household income	
< \$40,000	1154 (45.1)
\$40,000+	1403 (54.9)
Cancer-related characteristics	
Age at diagnosis (years)	
Mean ± SD	8.4 ± 5.6
Median	7.5
Range	0.0–21.8
Time since diagnosis (years)	
Mean ± SD	24.1 ± 8.2
Median	23.2
Range	10.2–48.3
Diagnosis	
Leukemia	1108 (37.3)
Lymphoma	612 (20.6)
CNS tumors	293 (9.9)
Neuroblastoma	193 (6.5)
Osteosarcoma/Ewing sarcoma	203 (6.8)
Wilms tumor	126 (4.2)
Retinoblastoma	88 (3.0)
Rhabdomyosarcoma	97 (3.3)
Other solid tumors (e.g., germ cell tumor, melanoma)	238 (8.0)

Table 1 (continued)

Other	11 (0.4)
Treatment history	
Chemotherapy	2547 (85.8)
Radiation therapy	1784 (60.1)
Surgery	1365 (46.0)
Amputation	109 (4.0)
Bone marrow transplant	127 (4.3)
Allogeneic/autologous	5 (0.2)
Allogeneic	62 (2.1)
Autologous	59 (2.0)
Relapse	333 (11.2)
Second cancer diagnosis	450 (15.2)
Age (Mean ± SD)	32.4 ± 11.0

For analytical purposes, diagnosis was combined into three groups: leukemia/lymphoma, CNS tumors, and other cancer diagnoses

the general civilian population. Indeed, when compared to other studies that utilized the PCL-C in a variety of settings (e.g., VA primary care, mothers of pediatric cancer survivors, bone marrow transplant recipients, etc.), prevalence rates of PTSS/PTSD ranged from 5 to 59% [16], suggesting that current findings are on the lower end of this spectrum.

Consistent with hypotheses and well-established risk factors for PTSS/PTSD in adult survivors of childhood cancer [11], females were more likely to report PTSS in comparison to males, and survivors with less than a college degree endorsed significantly higher levels of PTSS in comparison to those who graduated from college. Inconsistent with previous findings is that employment was not a significant predictor of PTSS in the current sample. Despite these risk factors, as expected, the majority of the adult survivors did not report clinically significant levels of PTSD symptoms, psychological distress, or cancer-related worry.

Also consistent with our hypothesis was the finding that, among those who identified a specific traumatic event, the majority of survivors (85.4%) reported a non-cancer-related event, compared to 14.5% who identified a cancer-related event as most traumatic. These rates are comparable to those observed in prior studies of long-term survivors that did not specifically orient participants to their cancer experience [13, 14]. This is perhaps more striking in the current study, given that the survivors had been brought back to the institution where they received their cancer treatment and were participating in research explicitly targeting them as cancer survivors. One might expect that answering questions about one's cancer treatment history could serve as a trigger for cancer-related memories, thus resulting in higher rates of those who report cancer as a traumatic event. However, this was not found. Notably, PCL-C scores were very similar between those who reported a cancer event and those who reported a non-cancer event. Taken together, such findings support hypotheses that childhood cancer is not a traumatic memory for most adult survivors, nor is it perceived as the most traumatic

Table 2 Descriptive statistics for the PCL-C, BSI, PSS, and Worry Questions

Measure	Mean ± SD	Median	% clinical range	Range
PTSD Checklist-Civilian (PCL-C)	27.7 ± 12.4	23.0	11.8 ^a	17.0–85.0
Brief Symptom Inventory (BSI)				
Global Symptoms Index (GSI)	50.0 ± 11.3	48.0	15.6 ^b	33.0–81.0
Perceived Stress Scale (PSS)	9.6 ± 3.5	9.0	–	4.0–20.0
Worry Questions	14.4 ± 4.8	15.0	–	5.0–25.0

^a Score ≥ 44

^b T-score, standardized mean = 50, SD = 10; clinically significant = $T \geq 63$

or stressful experience in their lives. As such, these findings support the change in the DSM-5 to no longer include a life-threatening illness as a qualifying event [31], and join others in suggesting that the medical traumatic stress framework is likely not appropriate for adult survivors of childhood cancer.

Findings from the current study are generally consistent with the broader literature that has found a variety of psychosocial-, biological-, and treatment-related factors that can place individuals at increased risk for developing PTSS/PTSD [14, 32–34]. Regarding survivors of CNS tumors, some findings suggest that brain tumors and CNS-directed treatment (i.e., cranial radiotherapy) are associated with long-term distress among adult survivors [35, 36]. In contrast, there is also evidence to suggest that levels of distress are lower in survivors of CNS tumors, which may be attributed to poor insight into their circumstances [37, 38]. Given the host of problems survivors of CNS tumors encounter [39], it is possible that PTSS is not a primary issue or target for intervention among this sub-population of survivors. Aside from diagnosis, other predictors of increased PTSS were primarily demographic or psychological in nature. This finding likely points to the natural variability of this construct in any sample, regardless of cancer history.

Findings from this study should be considered in light of limitations. First, the primary sources of data were self-report

surveys from individuals who elected to complete the questionnaires required for this study. Individuals who chose to participate may have under- or overrepresented their symptoms and those who did not choose to complete the necessary surveys may have done so because they did not feel these items applied to them (i.e., no concern for psychological distress) or because of severe symptomatology. Additionally, the way in which the items were organized did not cue participants to identify a traumatic event prior to answering questions regarding a traumatic experience. Though this eliminates the risk of a “focusing” effect, it makes the current findings difficult to compare to other studies that did ask for an event prior to completion of questions about PTSS/PTSD. Of note, participants were asked to describe an event after completing the PCL-C, and only a small proportion chose cancer. Relatedly, this study also did not have a control group, which somewhat limits the interpretation of findings, particularly with regards to how they compare to the general population. Lastly, among those who reported elevated levels of PTSS, there was no diagnostic follow-up to specifically assess for and ascertain the prevalence of PTSD.

Although the majority of participants did not endorse elevated rates of PTSS, 12% represents a critical minority that does report elevated PTSS. As such, while uniform screening for PTSS/PTSD may not be warranted, the use of a broad

Table 3 Influence of various factors for the outcome of psychological stress (PCL-C)

Predictor	Group	Estimate	Standard error	P value
GSI T-Score	1 unit	0.67	0.02	< 0.001
Worry total score	1 unit	0.10	0.03	0.001
PSS	1 unit	0.76	0.05	< 0.0001
Diagnostic category				
	CNS tumor vs. other	– 1.15	0.50	0.022
	Leukemia/lymphoma vs. other	0.12	0.31	0.69
Age at diagnosis	1 year	0.02	0.02	0.47
Gender	Female vs. male	1.64	0.28	< 0.0001
Education	< college graduate vs. ≥ college graduate	0.90	0.30	0.002

Scores on the PCL-C were associated with gender (females with more distress), education (less than college with more distress), and diagnostic category (CNS tumor with less distress). Higher scores on the other distress measures (GSI, Worry Scale, PSS) were also associated with higher PCL-C scores

GSI Global Stress Index, PSS Perceived Stress Scale, CNS central nervous system

screeener, such as the Brief Symptom Inventory (BSI) [22, 40] or the National Institutes of Health-designed Patient-Reported Outcomes Measure Information System [41], is an appropriate measure to utilize in a population of cancer survivors. Use of a screener that assesses general psychological distress would permit additional evaluation for those with significant elevations that are tailored to the individual's concerns/needs, including potential evaluation for PTSS/PTSD. When further assessment of PTSS/PTSD is called for with survivors, it is important to remember that the source of their distress may not be their cancer history, but rather an alternative and more salient traumatic event.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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