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Association of childhood trauma with fatigue, depression, stress, and inflammation in breast cancer patients undergoing radiotherapy

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Abstract

***Background*: This pilot study examined whether breast cancer patients with childhood trauma exhibit increased fatigue, depression, and stress in association with inflammation as a result of whole breast radiotherapy (RT).**

***Methods*: Twenty breast cancer patients were enrolled in a prospective, longitudinal study of fatigue, depression, and perceived stress prior to RT, week 6 of RT, and 6 weeks post-RT. Six weeks after RT, subjects completed the childhood trauma questionnaire (CTQ). Patients were also administered the multidimensional fatigue inventory, inventory of depressive symptomatology-self-reported, and perceived stress scale at all three time-points and underwent blood sampling prior to RT for gene expression and inflammatory markers previously associated with childhood trauma and behavioral symptoms in breast cancer patients.**

***Results*: Eight subjects (40%) had past childhood trauma (CTQ+). Compared to CTQ− patients, CTQ+ patients had significantly higher fatigue, depression, and stress scores before, during, and after RT ($p < 0.05$); however, RT did not increase these symptoms in either group. CTQ+ patients also exhibited increased baseline expression of gene transcripts related to inflammatory signaling, and baseline inflammatory markers including *c*-reactive protein, interleukin (IL)-6, and IL-1 receptor antagonist were positively correlated with depression, fatigue, and stress scores in CTQ+ but not CTQ− patients.**

***Conclusions*: Childhood trauma was prevalent and was associated with increased symptoms of fatigue, depression, and stress irrespective of RT. Increased symptoms in CTQ+ patients were also associated with baseline inflammatory markers. Treatments targeting childhood trauma and related inflammation may improve symptoms in breast cancer patients.**

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Introduction

Women with a history of childhood abuse and/or neglect are at increased risk for psychological distress when confronted with new traumatic experiences including a diagnosis and treatment of breast cancer [1]. Childhood abuse is common with one study demonstrating that 45% of patients seen in a primary care clinic have experienced some form of serious adverse childhood event [2].

Childhood abuse may have long-lasting effects on overall health including both physical and mental health [3]. Indeed, survivors of childhood abuse have been shown to experience significant fatigue, depression, and stress during challenging experiences or traumatic events that occur in adulthood [4].

Given the relationship between childhood abuse and mental health symptoms, previous studies have examined whether breast cancer patients with childhood trauma are particularly susceptible to cancer treatment-induced behavioral morbidities including fatigue, depression, and stress. These symptoms are the most common behavioral problems reported by breast cancer patients before, during, and after treatment [5]. Previous research indicates that a cancer diagnosis may trigger women with a history of childhood abuse to experience higher levels of intrusive cancer-related thoughts, images, emotions, and dreams during and after cancer treatment [1]. A study of breast cancer patients assessed after surgery and through early survivorship confirmed that childhood abuse predicted worse quality of life (QOL) as well as severe fatigue, depression, and stress during and after cancer therapy [4]. In addition, two cross-sectional studies of breast cancer survivors found that patients with childhood trauma reported worse QOL and greater persistent fatigue and psychological distress following cancer treatment compared to women without childhood abuse [6,7].

Breast radiotherapy (RT) following breast-conserving surgery is standard treatment for the majority of women with breast cancer. Fatigue, depression, and stress, affecting up to 40% of women, are commonly reported side effects of RT [8–12]. However, no previous study has examined whether a history of childhood trauma exacerbates the behavioral symptoms attributed to RT. The mechanism by which RT is associated with behavioral symptoms is poorly understood. However, breast cancer patients who develop fatigue and depression while undergoing RT have been found to exhibit elevated inflammatory markers including *c*-reactive protein (CRP), interleukin (IL)-6, IL-1-receptor antagonist (IL-1ra), soluble tumor necrosis factor receptor 2 (sTNFR2), and nuclear factor kappa B (NF-kB) DNA binding [9–14]. In addition, an association between inflammatory gene expression and depressive symptoms in breast cancer patients assessed before, during, and after RT has been reported [10]. Studies by our group and others have demonstrated that peripherally elaborated inflammatory cytokines can enter the brain and activate central inflammatory responses that are associated with altered basal ganglia dopamine metabolism, which is in turn associated with behavioral symptoms including depression and fatigue [15,16].

One pathway that may explain the relationship between childhood trauma and behavioral symptoms in patients undergoing cancer treatment is exacerbation of the inflammatory response. Previous studies have indicated that individuals with childhood trauma exhibit higher inflammatory markers as adults compared to individuals without childhood trauma [17,18]. These inflammatory markers have been correlated with depression [17,18]. One hypothesis is that childhood trauma precipitates a chronic inflammatory state that may further aggravate symptoms induced by breast cancer therapies like RT, leading to higher levels of fatigue, depression, and stress.

No previous study has longitudinally explored the influence of childhood trauma on fatigue, depression, and stress in women undergoing RT for breast cancer. Moreover, whether symptoms in patients with childhood trauma are associated with inflammatory markers is unknown. The purpose of this pilot study was to determine if breast cancer patients with childhood trauma are particularly susceptible to increased fatigue, depression, and stress during whole breast RT and whether these symptoms are associated with inflammation.

Methods

Participants

From March to September of 2010, 20 consenting patients were enrolled in this prospective, longitudinal study conducted in the Emory University Department of Radiation Oncology. The study was approved by the Emory University Institutional Review Board, and all patients provided written informed consent. Consecutive eligible patients were approached for enrollment to reduce enrollment bias, and the study was limited to 20 patients because of available funding.

To be eligible, patients were required to be women between the ages of 18–75 years with stage 0-IIIA breast cancer. Women with a history of schizophrenia, or bipolar disorder, or major depression and substance abuse/dependence within the past year were excluded.

All patients were treated with breast-conserving surgery followed by a standard radiation dose of 50 Gy to the whole breast followed by a 10 Gy boost. Study patients were evaluated at three-time points: baseline (1 week before radiation, T1), week 6 of radiation (T2), and 6 weeks after radiation (T3).

Behavioral assessments

Patients completed the childhood trauma questionnaire (CTQ) to assess history of childhood abuse and neglect. The CTQ was conducted in the absence of study staff at T3 in order to encourage open disclosure and minimize impact of the inventory on behavioral symptoms before and during RT. The CTQ is a 28-item survey that evaluates five subscales of trauma: physical, sexual, and emotional abuse, and physical and emotional neglect [19]. Moderate-to-severe cutoff scores are as follows: ≥13 for emotional abuse, ≥10 for physical abuse, ≥8 for sexual abuse, ≥15 for emotional neglect, and ≥10 for physical neglect [20]. If a subject had a score on any of the subscales representing moderate-to-severe trauma, these patients were considered to have clinically relevant childhood trauma (CTQ+).

Assessments of fatigue, depression, and stress were conducted at all time points. Fatigue was measured using the multidimensional fatigue inventory (MFI). The 20-item survey measures general, physical, and mental fatigue, including levels of activity and motivation [21]. A 10-point difference on the MFI has been established as criteria for a clinically meaningful difference in fatigue levels in patients receiving radiation [22]. The inventory of depressive symptomatology-self-reported (IDS-SR) was used to measure levels of depression. Scores ≥ 33 are indicative of moderate-to-severe depression [23]. Stress was measured using the perceived stress scale (PSS), a 10-item questionnaire [24,25]. All of the aforementioned instruments have been previously used in studies of breast cancer patients undergoing RT [22,26]. In order to minimize interviewer effects, patients completed all questionnaires in the absence of a treatment provider or study staff. After completing the instruments, research coordinators confirmed all questions were answered.

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Blood sampling

Peripheral blood was drawn prior to RT (T1) between 8–11 AM (to reduce circadian effects). Plasma was separated and stored at −80 °C until batch assay. Peripheral blood mononuclear cells (PBMCs) were isolated using density-gradient centrifugation and stored in freezing serum (90% fetal bovine serum, 10% dimethyl sulfoxide) at −80 °C until nuclear extraction for NF-kB DNA binding or mRNA isolation.

Microarray analysis of gene expression

Total RNA was extracted from ~10 million PBMCs and isolated using RNeasy kits (QIAGEN, Valencia, CA, USA) according to manufacturer instructions. After extraction, RNA samples were dissolved in RNAse-free water, and their concentrations and the A260/280 ratio were determined using the MBA 2000 system (Perkin-Elmer, Shelton, CT, USA). Each sample was linearly amplified by WT-ovation RNA amplification system (NuGEN Technologies, Inc., San Carlos, CA, USA) and was used for the microarray analysis at the Emory Cancer Genomics Shared Resource at Winship Cancer Institute. After hybridization to Illumina human HT-12 expression bead chips (Illumina, San Diego, CA, USA) that target over 47,000 probes, bead chips were scanned on the Illumina bead array reader to determine the probe fluorescence intensity. The raw probe intensities were then normalized by the quantile normalization algorithm [27].

Gene ontology (GO) and transcription factor bioinformatic analyses were conducted on genes that were differentially expressed in CTQ+ versus CTQ− patients. The purpose of this analysis was to determine whether patients with childhood trauma exhibited increased expression of genes involved in the inflammatory response. GO analysis was used to identify functional biologic processes that were over-represented in the differentially expressed genes. Transcription factor analysis was used to identify transcriptional regulatory pathways that may drive observed differences in gene expression. These methods are most accurate with relatively large numbers of genes that have large biologic differences in expression. Therefore, differentially regulated gene transcripts were identified using an effect size with a >20% difference (1.2-fold change), corresponding to a <10% false discovery rate [28,29] and a cutoff p value of 0.01, and then were subjected to the stringency of bioinformatic analyses to ensure statistical reliability. Differentially expressed transcripts were functionally annotated within pathways, and a network-based transcription factor analysis was conducted in metacore (GeneGo Inc., St. Joseph, MI, USA) [30]. The transcription factor analysis uses a transcriptional regulation algorithm to query a manually curated database and has been determined to be both accurate and comprehensive in identifying transcriptional regulatory pathways and target genes [31].

Nuclear factor kappa B DNA binding and downstream inflammatory markers

DNA binding of NF-kB in PBMCs was determined by enzyme-linked immunosorbent assay (ELISA) as previously described [32]. NF-kB DNA binding was performed in 16 of the 20 subjects based on sample availability/quality. Plasma sTNFR2 ($n=19$ subjects), IL-1ra ($n=19$ subjects), and IL-6 ($n=20$ subjects) were assayed in duplicates using sandwich ELISA (R & D Systems, Minneapolis, MN, USA). The mean inter-assay and intra-assay coefficients of variation were 10% or less. CRP ($n=20$ subjects) was measured by the immunoturbidometric method using the Beckman AU 480 chemistry analyzer and the ultra WR CRP reagent kit (Sekisui Diagnostics, Framingham, MA, USA). Inter-assay and intra-assay coefficients of variation were less than 3%.

Statistical analysis

Descriptive characteristics of the cohort including age, race, socioeconomic status, and tumor characteristics were compared in CTQ+ versus CTQ− subjects using independent t-tests or χ^2 tests (Table 1). General linear models were used to assess the effect of childhood trauma (CTQ+ versus CTQ−) on fatigue, depression, and stress scores over time (T1–T3). Comparisons of specific means of interest were conducted using Student–Newman–Keuls *post hoc* tests. Correlation analyses were used to determine whether severity of CTQ scores was associated with severity of symptoms and to assess relationships between symptoms and inflammatory markers in CTQ+ versus CTQ− patients. Where indicated, linear models were used to assess the effect of relevant covariates including age, BMI, education, marital status, cancer stage, and chemotherapy status, on significant relationships, and Holm's step-down procedure was used to adjust for multiple comparisons. Pearson's correlation coefficient was used for normally distributed data and Spearman's rho for non-normal data. Non-normal data were log transformed for statistical modeling. All p values were two-sided with 0.05 alpha level of significance. Statistical analyses were performed in SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Effect sizes (Cohen's d) and power calculations were performed using G*Power.

Results

Patient characteristics

Eight subjects (40%) were found to have a history of childhood trauma (CTQ+) with scores on at least one subscale indicating a history of abuse and/or neglect. Of the

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Table 1. Breast cancer patient and tumor characteristics by history of childhood trauma

Characteristic	No childhood trauma $N = 12$	Childhood trauma $N = 8$	p value
Age (SD)	57.0 (11.6)	47.4 (6.5)	0.03*
BMI (SD)	26.9 (4.2)	27.7 (7.3)	0.74
Race	–	–	0.69
Caucasian	8 (67%)	6 (75%)	–
Black people	4 (33%)	2 (25%)	–
Marital status	–	–	–
Single	1 (8%)	4 (50%)	0.08
Married	9 (75%)	4 (50%)	–
Divorced	2 (17%)	0 (0%)	–
Education	–	–	–
High School graduate	0 (0%)	3 (38%)	0.01*
Partial college	2 (17%)	3 (38%)	–
College graduate	2 (17%)	2 (25%)	–
Postgraduate training	8 (67%)	0 (0%)	–
Income	–	–	–
<$39,999	3 (25%)	1 (13%)	0.50
$40,000–$79,999	4 (33%)	4 (50%)	–
>$80,000	4 (33%)	1 (13%)	–
Unknown	1 (8%)	2 (25%)	–
Stage	–	–	–
0/I	7 (58%)	2 (25%)	0.14
II/III	5 (42%)	6 (75%)	–
Chemotherapy	–	–	–
No	4 (33%)	5 (63%)	0.20
Yes	8 (67%)	3 (38%)	–
Hormone	–	–	–
Yes	10 (83%)	5 (63%)	0.29
No	2 (17%)	3 (38%)	–
Receptor status	–	–	–
ER+	11 (92%)	6 (75%)	0.31
PR+	9 (75%)	6 (75%)	1.00
Her2/neu+	0 (0%)	2 (25%)	0.06

ER, estrogen receptor; PR, progesterone receptor; SD, standard deviation.
*$p < 0.05$

20 participants, 14 (70%) were Caucasian and six (30%) were African-American. Among all subjects, three (15%) received a high school diploma, five (25%) attended college without graduating, four (20%) completed college, and eight (40%) reported additional professional training and education beyond college. In our small cohort, CTQ+ women were less likely to have professional training or education beyond college ($p < 0.05$) than CTQ− patients. In addition, CTQ+ women were younger than CTQ− women [mean age 47 versus 57 years ($p < 0.05$)]. There were no other significant differences between the CTQ+ and CTQ− patients with respect to patient and tumor characteristics (Table 1).

Relationship between childhood trauma and behavioral symptoms

There was a significant main effect of CTQ status on all symptoms, with CTQ+ patients exhibiting significantly higher fatigue (MFI: F[1,18] = 5.1, $p = 0.04$, $d = 0.53$, Power = 0.70), depression (IDS-SR: F[1,18] = 7.2, $p = 0.015$, $d = 0.62$, Power = 0.83), and perceived stress (PSS; F[1,15] = 7.3, $p = 0.02$, $d = 0.70$, Power = 0.91) across all time points compared to CTQ− patients (Figure 1). *Post hoc* testing revealed statistically significant

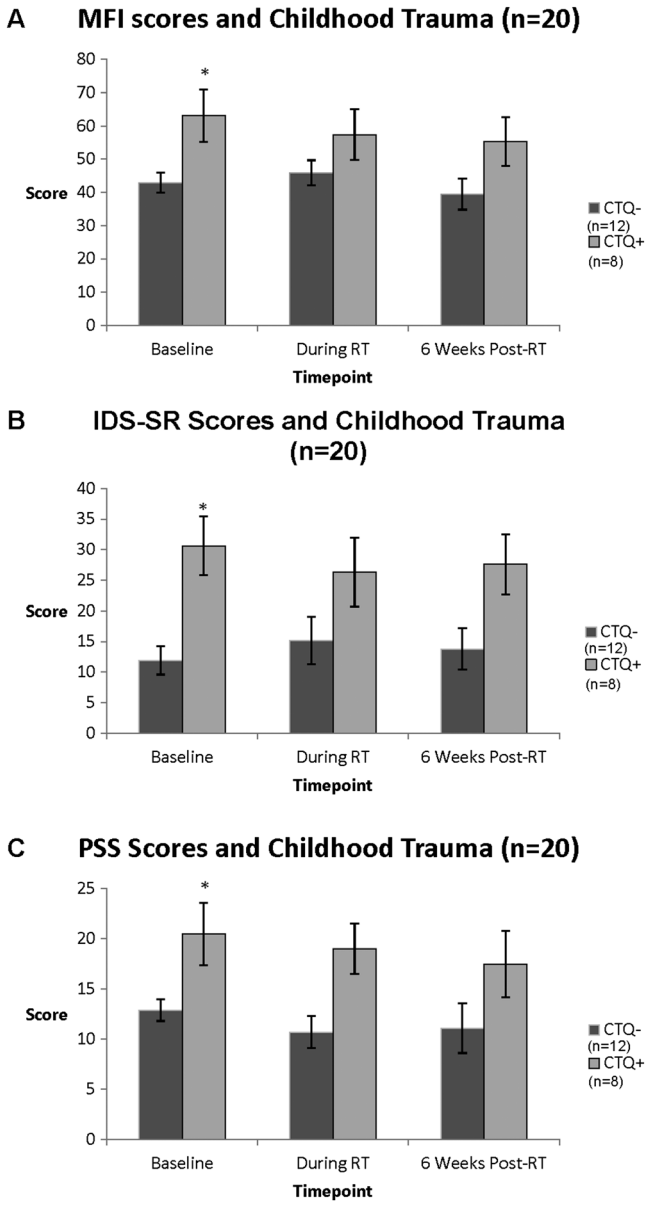

Figure 1. Symptom scores in breast cancer patients with and without childhood trauma. Women with (CTQ+) and without childhood trauma (CTQ−) completed the multidimensional fatigue inventory (MFI, a), inventory of depressive symptomatology-self reported (IDS-SR, b), and perceived stress scale (PSS, c) at baseline, during radiotherapy (RT) and 6 weeks post-RT. There was a significant main effect of childhood trauma on MFI, IDS-SR, and PSS scores, with CTQ+ patients exhibiting higher symptom scores across all time points (a–c) (all $p < 0.05$). RT did not significantly increase these symptoms to a greater extent in CTQ+ versus CTQ− patients. Data are presented as mean +/− standard error. *$p < 0.05$ (Student–Newman–Keuls *post hoc* test). CTQ, childhood trauma questionnaire.

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differences at baseline in all symptoms between CTQ+ versus CTQ− subjects ($p < 0.05$). Of note, 50% of CTQ+ patients versus 8% of CTQ− patients had IDS-SR scores ≥33 at some point during the study indicating moderate-to-severe depression. In addition, at each time point, the mean MFI score in CTQ+ patients was at least 10 points higher than the mean MFI score of CTQ− patients. Although there was a main effect of CTQ status on symptoms across time, there was no group by time interaction for any of the symptoms, indicating that RT did not significantly exacerbate fatigue, depression, or perceived stress differentially in CTQ+ versus CTQ− patients (Figure 1). Of note, the power for group (CTQ status) by time interactions was low for all behavioral measures (MFI = 0.22; IDS-SR = 0.49; PSS = 0.29), requiring a significantly larger sample size (~100 subjects total) to detect significant interactions if they were present.

Because there were no significant changes in behavioral symptoms as a function of RT, behavioral scores prior to RT were used to assess potential effects of covariates on the relationship between childhood trauma and behavioral scores and to examine relationships between the severity of reported trauma and severity of symptoms. Due to the small sample size, covariates including age, BMI, education, marital status, stage of cancer, and chemotherapy status were entered independently into models including behavioral scores as the dependent variable and CTQ status as a predictor variable. The relationship between PSS scores and CTQ remained significant after correction with all covariates. However, marital status reduced the significance of the effect of childhood trauma on MFI scores to $p = 0.06$. Marital status, cancer stage, and age reduced the significance of the association between childhood trauma and IDS-SR scores to $p = 0.18$, $p = 0.08$, and $p = 0.12$, respectively. Regression analyses examining relationships between severity of CTQ scores with fatigue, depression, and perceived stress prior to RT revealed significant positive associations between CTQ severity with IDS-SR ($r = 0.45$, $df = 18$, $p = 0.048$) and PSS ($r = 0.49$, $df = 18$, $p = 0.027$), but not MFI ($r = 0.39$, $df = 18$, $p = 0.09$) scores. CTQ severity remained the most significant predictor of PSS, but not IDS-SR, scores after controlling for covariates in both forward and backward linear regression analyses.

Inflammatory markers and gene expression in patients with childhood trauma

Relationships between inflammatory markers obtained at baseline and behavioral symptoms at T1–T3 in CTQ+ and CTQ− patients were explored. As shown in Table 2, in CTQ +, but not CTQ− patients, significant positive correlations were found between MFI and CRP ($p = 0.021$) and IL-6 ($p = 0.004$) at T1. In addition, in CTQ+, but not CTQ− patients, a significant correlation was found between IDS-SR scores and CRP ($p = 0.001$), IL-6 ($p = 0.037$), and IL-1ra ($p = 0.001$) at T1. Finally, PSS scores correlated with CRP ($p = 0.015$) and IL-6 ($p = 0.047$) in CTQ+ but not CTQ− patients at T1. Among CTQ+ patients, relationships between MFI scores with IL-6, and IDS-SR scores with CRP and IL-1ra remained significant after adjustment for comparison of multiple inflammatory biomarkers. Due to non-normality of the inflammatory biomarker data and the small sample size, statistical modeling with covariates was not conducted in this exploratory analysis. Of note, baseline CRP, IL-6, and IL-1ra were also variably associated with MFI, IDS-SR, and PSS scores at T2 and T3 (Table 2). No significant correlations between symptoms and sTNFR2 or NF-kB DNA binding at baseline were found at T1–T3 in CTQ+ or CTQ− subjects.

Table 2. Correlations between baseline inflammatory markers and symptom scores throughout the study in patients with childhood trauma ($n = 8$)

MFI	CRP (T1)	IL-6 (T1)	IL-1ra (T1)
T1	0.786*	0.881**	0.667
T2	0.714*	0.619	0.714*
T3	0.762*	0.667	0.881**
IDS-SR	–	–	–
T1	0.929**	0.738*	0.929**
T2	0.515	0.419	0.551
T3	0.786*	0.571	0.857**
PSS	–	–	–
T1	0.810*	0.714*	0.690
T2	0.643	0.429	0.750
T3	0.819*	0.699	0.783*

MFI, multidimensional fatigue inventory; IDS-SR, inventory of depressive symptoms-self reported; PSS, perceived stress scale; CRP, *c*-reactive protein; IL, interleukin; ra, receptor antagonist; T1, before radiation; T2, week 6 of radiation; T3, 6 weeks after radiation. All correlations are Spearman's correlation coefficients.
*$p < 0.05$.
**$p < 0.01$.

Gene expression differences in CTQ+ versus CTQ− patients were examined at baseline. One hundred eighty-five gene transcripts were differentially expressed in CTQ+ versus CTQ− patients: 166 were up-regulated and 19 were down-regulated (see Supplemental Table S1 for the list of differentially expressed genes). CTQ+ patients exhibited alterations in gene transcripts related to inflammatory signaling including IL-22, IL-17, and C-C chemokine receptor 5 signaling in macrophages and *T* lymphocytes.

Metacore analysis of transcription factor pathways differentially expressed in CTQ+ versus CTQ− patients revealed an over-representation of genes regulated by the NF-kB family transcription factor, RelA (p65 subunit of NF-kB; $Z = 107.44$, $p = 3.08e\text{-}67$). Transcription factor analysis of all differentially expressed genes identified 26 NF-kB-regulated genes (22 up-regulated and 4 down-regulated).

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Conclusions

This study examined the impact of whole breast RT on behavioral symptoms in breast cancer patients with a history of childhood abuse. We found that a history of childhood abuse was common in our breast cancer patients and a history of childhood trauma was associated with clinically significant higher fatigue and depression scores before, during, and after RT. Nevertheless, while CTQ+ women had higher levels of fatigue, depression, and perceived stress across all time points, RT did not significantly worsen these symptoms in CTQ+ versus CTQ− women. Childhood trauma was also associated with increased expression of genes associated with inflammatory signaling pathways and transcription factors related to NF-kB, and symptoms in CTQ+ patients during the study were associated with baseline CRP, IL-6, and IL-1ra in CTQ+ but not CTQ− subjects.

One previous study assessed breast cancer patients with or without childhood abuse shortly after surgery and at four subsequent time points over a 9-month period. These patients underwent a variety of adjuvant breast cancer treatments. Similar to the current study, the investigators found that a history of childhood adversity was associated with increased fatigue, depression, and perceived stress before and during breast cancer treatment but there appeared to be no additional effect of treatment variables including RT, type of surgery, time since surgery, and endocrine therapy [4]. Interestingly, in our study, only the relationship between CTQ status and PSS scores remained significant after adjustment for all covariates. However, the small sample size greatly limited the potential for statistical modeling, and the group effects of CTQ status on fatigue and depression scores had large effect sizes ($d = 0.53$ and $d = 0.62$, respectively).

The biological mechanisms underlying susceptibility to fatigue and depression in CTQ+ patients undergoing RT warrant consideration. Previous studies have shown that childhood trauma may alter neurocircuity within the brain during a time when the brain is potentially vulnerable to environmental stressors [33–35]. In addition, childhood abuse has been associated with elevated markers of inflammation including CRP, IL-6, and TNF-alpha, in adults. These biomarkers have also been correlated with fatigue and depression in breast cancer patients during and after treatment including RT [10,13,36]. Although our study showed no effect of RT on behavioral symptoms, it is apparent that baseline inflammation related to childhood abuse/neglect was associated with increased depression, fatigue, and stress before, during, and after RT in CTQ+ patients. Previous studies have proposed that patients exposed to childhood trauma may experience a 'biological embedding' of stress through inflammatory processes in childhood [37]. This increased inflammatory tone in CTQ+ patients may interact with stressors of diagnosis, surgery, and chemotherapy in breast cancer to produce behavioral symptoms prior to, during, and after RT.

A primary limitation of this study is the small sample size. Although sufficient power was apparent to detect significant differences between groups (CTQ+ versus CTQ−) across time, power for detecting interactions between group and time (which would account for the effects of RT) was low, ranging from 0.22–0.49. Thus, future studies with larger patient numbers are needed to definitively determine whether significant interactions between childhood trauma and RT lead to greater symptoms.

In conclusion, the findings emphasize the need to screen and identify patients affected by childhood trauma early in the course of breast cancer treatment and to provide them proper psychological and medical support, which may include counseling and evaluation and management of an increased inflammatory status.

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Ethics approval

The study was conducted within the ethical guidelines espoused by Emory University and the IRB.

Conflict of interest

The authors have declared no conflicts of interest.

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Supporting information

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