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Lauren Brown March 25, 2020

Potential Effects of Breast Cancer on PTSD Symptoms in a Trauma-Exposed Population of African American Women

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Abstract

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Breast cancer accounts for approximately a quarter of all cancer cases in women, and the long-term effects of the stress from diagnosis and treatment can result in adverse mental health outcomes that range from fear of cancer recurrence to PTSD. There are numerous known risk factors for PTSD, but this study aimed to identify risk factors specific to trauma-exposed African American women with breast cancer. We performed a retrospective analysis to see how diagnosis features, treatment methods, and inflammatory biomarkers are associated with PTSD and depression symptoms. Of significance, we found that women diagnosed with early-stage breast cancer had greater PTSD hyperarousal symptoms, women who did not receive radiation had greater PTSD total, intrusive, and hyperarousal symptoms, women who did not receive chemotherapy had greater depression symptoms, women who have any form of systemic therapy have fewer PTSD total, PTSD avoidance, and depression symptoms, and obese women have greater PTSD intrusive symptoms. We also found that chemotherapy has a positive association with depression symptoms and years since diagnosis. Finally, we found serum chloride to have a quadratic relationship with depression symptoms. These findings were largely contrary to our hypotheses, but they suggest that many factors surrounding breast cancer diagnosis, treatment, and inflammation may uniquely modulate the fear response in African American women at high risk for PTSD.

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Introduction

Breast cancer is the most common type of cancer diagnosed in women, with approximately a quarter of all cancer diagnoses in women being breast cancer (Bray et al., 2018; Jemal et al., 2010; Siegel et al., 2016). Despite the many treatment options, breast cancer causes around 14% of all cancer-related deaths in women (Siegel et al., 2016). Not surprisingly, the diagnosis and treatment of breast cancer can be stressful both physically and psychologically, and this stress exposure of diagnosis and treatment can persist and result in fear responses that range from fear of progression (FoP) and fear of cancer recurrence (FCR) to post-traumatic stress disorder (PTSD) (Arnaboldi et al., 2017; Brown et al., n.d.; Mehnert et al., 2009; Simard et al., 2013).

Diagnosis with a life-threatening illness is one of the many types of trauma exposures that can lead to the development of PTSD and is considered a criterion A stressor (American Psychiatric Association, 2013; Cohn et al., 2018; Gradus et al., 2015). While breast cancer can be life-threatening, there is debate about whether or not all breast cancer diagnoses are sufficient to meet diagnostic criteria for PTSD (Arnaboldi et al., 2017). The Diagnostic and Statistical Manual (DSM)-V states that the diagnosis of a life-threatening illness, such as breast cancer, must be both “sudden” and “catastrophic” in order to meet diagnostic criteria for PTSD (American Psychiatric Association, 2013; Arnaboldi et al., 2017). Because in most women a breast cancer diagnosis is sudden, disruptive, and life-threatening (Cordova et al., 2007), for the purposes of the current investigation, we will consider breast cancer diagnosis and treatment to be sufficiently stressful events that can lead to the development of PTSD (Brown et al., n.d.).

A diagnosis with any type of cancer increases one’s lifetime risk for PTSD by a factor of 1.66, as compared to cancer-free controls who differ only by their lack of exposure to cancer and

cancer treatment, and this may have implications on long-term effects of cancer diagnosis and treatment (Swartzman et al., 2017). Regarding breast cancer specifically, approximately 10% of women develop PTSD following a diagnosis with breast cancer (Swartzman et al., 2017). However, this statistic varies depending on each study's inclusion criteria and methodology, so some studies report 0% PTSD following breast cancer diagnosis while others report up to 32.3% (Arnaboldi et al., 2017). This wide range implies that there may be variability in how the stress of breast cancer diagnosis and treatment impacts each patient, and that factors unrelated to the diagnosis and treatment may also be involved in contributing to a patient's risk for PTSD following a breast cancer diagnosis (Brown et al., n.d.).

PTSD is a trauma- and stress-related disorder that occurs as a result of traumatic experiences, and it is characterized by symptoms of intrusion, avoidance, negative mood, and alterations in arousal (American Psychiatric Association, 2013). On average in the United States, there is a lifetime prevalence of PTSD that is approximately 7.8%, but only about a third of the people with PTSD recover from the disorder (Ronald C. Kessler et al., 1995). This can be particularly harmful because PTSD can impact patients' lives in ways beyond the stress of the disorder, such as leading to increased medication nonadherence (both skipping and forgetting), smoking, and suicidal ideation (R. C. Kessler, 2000; Zen et al., 2012). As such, the prevention and treatment of PTSD are critical, and early identification of patients at high risk for the disorder may help to prevent or alleviate their suffering (Brown et al., n.d.).

The risk for PTSD in the general population is not uniform, as there are a number of social, biological, and genetic risk factors that can increase one's risk of developing PTSD. In civilian populations, meta-analytic evidence indicates that the strongest known risk factors for PTSD are childhood abuse and familial or personal history of psychiatric disorders (Brewin,

2005; Brewin et al., 2000; Ozer et al., 2003). Other notable risk factors include sex, race, education level, childhood adversity, and lack of social support following the trauma (Abbey et al., 2015; Brewin et al., 2000). These risk factors likely contribute to the high proportion of PTSD that is observed at Grady Memorial Hospital in Atlanta, Georgia. At Grady Memorial Hospital, the lifetime prevalence of PTSD is 46.2%, with females being twice as likely as males to develop PTSD (Gillespie et al., 2009; Ronald C. Kessler et al., 1995). This specific population of females is therefore at a very high risk for PTSD relative to the rest of the population. In the current study, we investigated the relationship between potential risk factors and PTSD symptom severity among breast cancer survivors and a cancer-free control group.

There are also a number of known risk factors for PTSD that are specific to women diagnosed with breast cancer. The primary known risk factor for PTSD in this population is the severity of the breast cancer diagnosis, with women who are diagnosed with more advanced breast cancer (higher stage) being at greater risk for developing PTSD than women diagnosed with less advanced breast cancer (Abbey et al., 2015; S. K. Smith et al., 2011). When investigating survivors of breast cancer, minority racial and ethnic groups are at greater risk for developing PTSD than non-minority women (WU et al., 2016). Age also modulates risk such that women who were younger than 50 years old at the time of diagnosis were more likely to develop PTSD than women who were older than 70 years old at the time of diagnosis (Vin-Raviv et al., 2013). Prior life stress and trauma exposure can also increase one's risk for developing PTSD, with previous trauma increasing the chance of developing PTSD by a factor of two (Breslau et al., 1999). This includes, but is not limited to, childhood trauma and neglect, which also alter a woman's ability to cope with breast cancer (Guveli et al., 2017).

Potential biological mechanisms that may link breast cancer and PTSD include the role of the inflammatory response and the role of ovarian hormones (Brown et al., n.d.). People with PTSD are have been shown to have higher levels of pro-inflammatory mediators (such as TNF-α, IL-1b, and IL-6) as well as lower levels of anti-inflammatory markers compared to healthy controls (Brown et al., n.d.; Michopoulos et al., 2017; Passos et al., 2015). Chronic inflammation promotes cancer by contributing to proliferation, survival, angiogenesis, and metastasis of cancer cells (Mantovani et al., 2008). Because inflammation is characteristic of both cancer and PTSD, it may be a mechanism by which the conditions influence one another (Rustad et al., 2012). Some other commonly measured biological markers in the blood that may have a role in exacerbating or protecting against PTSD include neutrophils (Andrews & Neises, 2012), lymphocytes (Wilson et al., 1999), chloride (Vasterling & Brewin, 2005), glucose (Baker et al., 2012), and hematocrit (Lindqvist et al., 2017). These immune-related biomarkers are relevant because neutrophils and lymphocytes are direct indicators of immune function (Leliefeld et al., 2015), and chloride, glucose, and hematocrit may indicate major medical conditions that could contribute to heightened inflammation (Barzilay et al., 2001; Eichner, 1973; Schaer, 1999).

The heightened inflammation observed in both PTSD and breast cancer may also be partly related to diet and obesity, particularly obesity-associated inflammation (Brown et al., n.d.; Cleary & Grossmann, 2009; Scott et al., 2008; Zass et al., 2017). Obesity is defined as having a body mass index (BMI) ≥ 30, and obesity-associated inflammation is likely due to the metabolites being produced by the adipocytes (Kolb et al., 2016). In addition to obesity increasing one's risk for breast cancer diagnosis, obesity also increases the risk of metastasis and poor clinical outcome (Kolb et al., 2016). Aside from inflammation, another major component that connects breast cancer and obesity is the upregulation of estrogens from adipocytes, which is

a leading hypothesis for why women who are obese have increased estrogen-receptor positive (ER+) breast cancer (Cleary & Grossmann, 2009; Kolb et al., 2016).

This relates directly to an aspect of breast cancer that makes it unique from other cancers: its relationship with ovarian hormones, particularly estrogens (Osborne et al., 1980). Of the women with invasive breast cancer diagnoses, approximately 79% are ER+ (DeSantis et al., 2019). The presence or absence of these hormone receptors, as well as progesterone receptors (PR) and human epidermal growth factor 2 (HER2) receptors, can influence the course of treatment (Nguyen et al., 2008). While cancer is commonly treated with a combination of chemotherapy, radiation, and surgery, many treatments unique to breast cancer are aimed at inhibiting hormone receptors.

The most common anti-endocrine therapies for ER+ breast cancer target either estrogen receptors or systemic estrogens. Selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs) inhibit hormone-responsive tumor growth by preventing the estrogens from binding to the receptors, whereas aromatase inhibitors work by decreasing the amount of available systemic estrogens (Komm & Mirkin, 2014; Pickar et al., 2018; I. E. Smith, 2003). However, these treatments are not isolated to targeting the tumor and can block estrogen binding throughout the entire body, ultimately disrupting ovarian function (Lumachi et al., 2013; Mourits, 2001). One example is tamoxifen, which is a commonly prescribed SERM that has been shown to disrupt ovarian function such that serum estrogen and progesterone levels are increased and ovulation is induced (Mourits, 2001). Because natural hormonal cycling is important in regulating emotion in women, anti-endocrine therapies may also have significant effects on brain circuitry (Derntl et al., 2008; Walf & Frye, 2006). Anti-endocrine therapies may also influence fear extinction, as low estrogen levels have a demonstrated role in reducing fear extinction and

therefore may increase the risk for PTSD (Brown et al., n.d.; Garcia et al., 2018; Glover et al., 2012).

Another reason it is critical to address PTSD risk in breast cancer patients is that PTSD is often comorbid with other mental health disorders such as major depressive disorder (MDD) (Angelakis & Nixon, 2015). More specifically, breast cancer patients who are diagnosed with cancer-related PTSD are more likely to also be diagnosed with major depression, dysthymic disorder, or generalized anxiety disorder than patients who are not diagnosed with cancer-related PTSD (Mehnert & Koch, 2007). Because patients who are diagnosed with either PTSD alone or PTSD comorbid with other mental disorders are more likely to experience poorer functioning and lower quality of life (Shelby et al., 2008), it is critical to identify the women who are at heightened risk for adverse mental health outcome following breast cancer diagnosis so that preventative measures can be taken to protect their mental health. For this reason, our investigation includes analysis of depression symptoms in addition to PTSD symptoms.

Based on these well-known and hypothesized risk factors for PTSD development in women diagnosed with breast cancer, the primary aim of the current study was to investigate how breast cancer diagnosis and treatment may affect PTSD symptoms in a high-risk trauma-exposed population of African American women. Our approach involved a broad, retrospective analysis of women with breast cancer trauma within a larger study of PTSD in a civilian population. There were three main components of breast cancer that were of interest in this study: diagnosis-related factors, treatment mechanisms, and inflammation.

Of the factors surrounding breast cancer diagnosis, we chose to investigate how the age of diagnosis, current hormonal status (pre- or post-menopause), and the severity of cancer (as assessed by stage) impacted PTSD and depression symptoms. Based on the findings of

Vin-Raviv et al. (2013), we hypothesized that women who were younger than 50 at the time of diagnosis would have greater PTSD and depression symptoms than women who were older than 50 at the time of diagnosis. Regarding hormonal status, we hypothesized that post-menopausal women would have greater PTSD and depression symptoms than pre-menopausal women due to the greater total suppression of ovarian hormones (Thewes et al., 2004). Finally, we hypothesized that women who were diagnosed with late-stage breast cancer would have more PTSD and depression symptoms than women diagnosed with early-stage breast cancer (Abbey et al., 2015; S. K. Smith et al., 2011).

Regarding breast cancer treatment mechanisms on PTSD symptoms, we assessed how surgery type, chemotherapy, radiation, anti-endocrine therapy, and systemic therapies were associated with PTSD and depression symptoms. We hypothesized that women who received a mastectomy would have greater PTSD and depression symptoms than women who received a lumpectomy, following (Moyer & Salovey, 1996). We also hypothesized that women who received chemotherapy would have greater PTSD and depression symptoms than women who did not receive chemotherapy (Pandey et al., 2006). Similarly, based on the finding of increased arousal and anxiety with radiation therapy, we hypothesized that women who received radiation would have greater PTSD and depression symptoms (Andersen et al., 1984). Given the findings of adverse mental health outcomes following treatment with SERMs and aromatase inhibitors (Lumachi et al., 2013; Mook et al., 2005; Rocha-Cadman et al., 2012), we hypothesized that treatment with anti-endocrine therapy would be associated with greater PTSD and depression symptoms. Given the hypothesized increase of PTSD and depression symptoms following both chemotherapy and anti-endocrine therapy, which are

both systemic therapies, we hypothesized that women who received any type of systemic therapy with have greater PTSD and depression symptoms than women who did not.

Finally, to assess the role of inflammation in PTSD symptom severity, we investigated the association of obesity and different blood biomarkers (chloride, glucose, neutrophils, lymphocytes, and hematocrit) with PTSD and depression symptoms. Given previous findings (Scott et al., 2008), we hypothesized that obesity would be associated with greater PTSD and depression symptoms. Although analyzing the blood biomarkers was largely exploratory, we hypothesized that normal levels of chloride, high levels of neutrophils, normal levels of hematocrit, low levels of glucose, and high levels of lymphocytes would correlate with greater PTSD and depression symptoms.

Methods

Participant Recruitment

Participants were randomly recruited in waiting rooms at Grady Memorial Hospital and interviewed for trauma history and current emotional state via questionnaires such as the PTSD Symptom Scale (PSS) and Beck's Depression Inventory (BDI). Of the full sample of n=10,844, there were n=6,196 African American women who had complete PSS data. Of these 6,196 women, the women who had breast cancer were identified by searching within the traumatic events inventory (TEI) for participants who endorsed breast cancer diagnosis and treatment as an experience of trauma exposure (N=49). A randomized case-matching procedure ("Fuzzy Match" in SPSS 24.0) was used to match these 49 women with 49 cancer-free control participants, based on age (fuzz factor of 5 years) and number of prior trauma exposures (fuzz factor of 0) (Table 1).

The two relevant emotional state questionnaires to this study were the PSS and BDI. The PSS is shorter and more easily administered than the Clinician-Administered PTSD Scale (CAPS), and is demonstrated to be "reliable and valid in civilian trauma survivors" (Foa & Tolin, 2000)(Foa et al., 1993). The PSS consists of 17 items, with each item relating to one of three PTSD symptom clusters: intrusion, avoidance, or hyperarousal (Foa & Tolin, 2000). As such, PTSD symptoms can be evaluated in total or with respect to each symptom cluster. The other measure utilized in this study was the BDI, a self-report measure that has shown to have high content validity and high internal consistency for the assessment of depression symptom severity (Richter et al., 1998). The purpose of evaluating depression is to have a better understanding of the broader implications of how breast cancer diagnosis and treatment may impact PTSD symptoms, including comorbidity with depression symptoms. While neither of these assessments are diagnostic, they provide valid insight into the participants' emotional state following traumatic events.

Medical Record Analysis

Medical record review allowed for data collection relating to details of breast cancer diagnosis, breast cancer treatment, and blood chemistry. Participants' records were analyzed for date of breast cancer diagnosis, the severity of cancer diagnosis (stage and grade), receptors on the breast cancer tumor (ER, PR, HER2), surgery type (mastectomy, lumpectomy, etc.), chemotherapy, radiation, anti-endocrine therapies, and blood chemistry (chloride, glucose, hematocrit, lymphocytes, and neutrophils). Blood chemistry data were collected for the time point closest to that of the interview.

Statistical Analyses

All statistical analyses were conducted using IBM SPSS 24.0. When necessary, data were normalized by taking the logarithm. The tests used were two-tailed Student's t-test for independent samples, univariate ANOVA, regression analysis, and scatterplot. The results are presented as means followed by SEM, and statistical significance was set at $p \leq 0.05$.

Results

Demographic and Diagnosis Factors

When comparing women who had breast cancer to cancer-free trauma controls, we found no significant difference in PTSD or depression symptoms between the two groups, $p > 0.05$ (Figure 1). Further, when looking at the hormonal status of pre-menopausal versus post-menopausal, women who were post-menopausal appeared to have fewer total PTSD symptoms than women who were pre-menopausal; however, this was not a significant difference, $p > 0.05$ (Figure 2).

When investigating whether or not breast cancer diagnosis factors can impact PTSD and depression symptoms, our data showed no significant differences in women who were younger in age at the time of cancer diagnosis (<50 years old) compared to women who were older in age at the time of cancer diagnosis (>50 years old) with respect to total PTSD symptoms, PTSD intrusive symptoms, PTSD avoidance symptoms, PTSD hyperarousal symptoms, or depression symptoms (all *p's* > 0.05) (Figure 3). When investigating the potential effect of cancer stage on PTSD and depression symptoms, women were grouped as having either early-stage (stage 0, 1, or 2) or late-stage (stage 3 or 4) breast cancer. The women with early-stage breast cancer had higher PTSD hyperarousal symptoms than women who were diagnosed with late-stage breast

cancer (early-stage: $M = 6.09$, $SEM = 0.99$, late-stage: $M = 1.87$, $SEM = 0.80$; $t(27) = 2.20$, $p = 0.04$; Cohen's D = 4.90; Figure 4). There was also no significant difference in total PTSD, PTSD intrusive, PTSD avoidance, or depression symptoms based on early versus late stage of diagnosis (all p's > 0.05). We also found no significant differences in PTSD or depression symptoms based on the specific subtype of breast cancer (basal, luminal, etc.) (all p's > 0.05).

Cancer Treatment

When comparing the effects of a lumpectomy versus a partial or full mastectomy on PTSD and depression symptoms, we found no significant difference in symptom severity. That being said, we did find that women who received radiation had lower PSS hyperarousal scores than women who did not receive radiation (radiation: $M = 4.18$, $SEM = 4.58$, no radiation: $M = 8.25$, $SEM = 3.37$; $t(28) = 2.29$, $p = 0.03$; Cohen's D = 1.01; Figure 5). Women who received radiation also had lower PSS total than women who did not receive radiation (radiation: $M = 11.92$, $SEM = 12.85$, no radiation: $M = 21.88$, $SEM = 8.92$; $t(28) = 2.01$, $p = 0.05$; Cohen's D = 0.90; Figure 5). Finally, women who received radiation had lower PSS intrusive scores compared to women who did not receive radiation (radiation: $M = 12.44$, $SEM = 12.57$, no radiation: $M = 21.71$, $SEM = 5.56$; $t(28) = 2.04$, $p = 0.05$; Cohen's D = 0.84; Figure 5). There was no significant difference in PSS avoidance or BDI scores based on radiation treatment (both p's > 0.05).

While this sample showed no effect of anti-endocrine therapy on PTSD symptoms, it was found that women who received chemotherapy had lower BDI scores than those who did not receive chemotherapy (chemotherapy: $M = 9.57$, $SEM = 7.78$, no chemotherapy: $M = 19.43$, $SEM = 14.32$; $t(28) = 2.38$, $p = 0.02$; Cohen's D = 0.86; Figure 6). There were no significant differences in PSS total, PSS intrusive, PSS avoidance, or PSS hyperarousal based on chemotherapy (all p's > 0.05). As both anti-endocrine therapies and chemotherapies are systemic

therapies, whereas surgery and radiation are locally targeted, an analysis was also performed to determine if the effect had to do with whether or not the treatment was systemic. When analyzing women who received any systemic therapy versus those who did not, it was found that women who received a systemic therapy had lower PSS total (systemic therapy: $M = 11.35$, $SEM = 2.23$, no systemic therapy: $M = 22.80$, $SEM = 4.99$; $t(29) = 2.40$, $p = 0.02$; Cohen's D = 0.91), PSS avoidance (systemic therapy: $M = 3.35$, $SEM = 0.87$, no systemic therapy: $M = 9.50$, $SEM = 1.72$; $t(29) = 3.44$, $p = 0.002$; Cohen's D = 1.36), and BDI scores (systemic therapy: $M = 9.78$, $SEM = 1.57$, no systemic therapy: $M = 24.89$, $SEM = 4.87$; $t(29) = 3.86$, $p = 0.001$; Cohen's D = 1.31) than women who did not receive a form of systemic therapy (Figure 7). There were no significant differences in PSS intrusive or PSS hyperarousal based on systemic therapy *(all p's* > 0.05).

Between the date of breast cancer diagnosis and the date that the interview was conducted, there was an average of 70.61 months ± 14.24 months, so many women had a long delay between breast cancer treatment and our evaluation of their PTSD and depression symptoms. When looking at how symptoms trend as a function over time, women who received chemotherapy showed no association between BDI score and years since diagnosis, whereas women who did not receive chemotherapy showed a positive association between BDI scores and years since diagnosis (Figure 8).

Multiple linear regression analyses were used to predict PSS total, PSS intrusive, PSS avoidance, PSS hyperarousal, and BDI symptoms based on years since diagnosis, current age, chemotherapy, radiation, and endocrine therapy. Years since diagnosis ($p = 0.02$, $\beta = 0.32$), age ($p = 0.03$, $\beta = -0.30$), and chemotherapy ($p = 0.05$, $\beta = -0.33$) were each significant predictors of PTSD hyperarousal symptoms. Current age ($p = 0.01$, $\beta = -0.41$) and chemotherapy ($p = 0.01$, β

= -0.48) were both significant predictors of BDI scores. Years since diagnosis, current age, chemotherapy, radiation, and endocrine therapy were not significant predictors of PTSD total, PTSD intrusive, or PTSD avoidance symptoms (all *p's* > 0.05). Current age, radiation, and endocrine therapy were not significant predictors of PTSD hyperarousal symptoms (all *p's* > 0.05). Years since diagnosis, radiation, and endocrine therapy were not significant predictors of BDI scores (all *p's* > 0.05).

Inflammation: Obesity and Blood Chemistry

Of the women who had breast cancer, obesity was positively associated with greater intrusive PTSD symptoms (obese: $M = 4.30$, $SEM = 0.98$, non-obese: $M = 1.56$, $SEM = 0.56$; $t(27) = -2.43$, $p = 0.02$; Cohen's D = 0.82; Figure 9). There was no significant difference between PTSD total, PTSD avoidance, PTSD hyperarousal, or BDI based on BMI (all *p's* > 0.05). Blood chemistry data were collected for the group with breast cancer as well as the trauma-matched cancer-free control group, $M = 2.50$, $SEM = 0.36$ months from the time of the interview. Chloride showed a quadratic relationship with BDI score, such that high and low values outside the normal range for chloride (<97 or >107 mmol/L) corresponded with lower BDI scores (Figure 10). This result was similar for both cancer participants (R^2=0.05) and control participants (R^2=0.08). The other four blood chemistry markers were not significantly associated with PTSD or depression symptom severity (all *p's* > 0.05).

Discussion

The current project investigated the influence of breast cancer diagnosis and treatment on PTSD and depression symptoms in a population of African American women at high risk for PTSD. While our hypothesis about the age of diagnosis was supported, our hypotheses about

hormonal status and stage of diagnosis were both not supported in this study. Regarding treatment mechanisms on PTSD symptoms, we assessed how surgery type, chemotherapy, radiation, anti-endocrine therapy, and systemic therapies were associated with PTSD and depression symptoms and each of our hypotheses was not supported. Finally, our hypothesis regarding obesity and PTSD and depression symptoms was confirmed, and the blood biomarkers were largely not confirmed with the exception of chloride's quadratic correlation with depression. While these findings were largely contrary to our hypotheses, they suggest that many factors surrounding breast cancer diagnosis, treatment, and inflammation may uniquely modulate the fear response in African American women at high risk for PTSD.

Demographic and Diagnosis Factors

Cancer and cancer-free control groups showed no differences in PTSD symptom severity when both trauma history and age were controlled for, indicating that breast cancer has similar mental health impacts relative to other types of trauma exposures. These data support the idea that breast cancer is an impactful trauma that can contribute to PTSD symptoms in this population of women. Regarding hormonal status, we hypothesized that post-menopausal women would have greater PTSD and depression symptoms than pre-menopausal women due to the greater total suppression of ovarian hormones (Thewes et al., 2004). Our results ran contrary to this hypothesis, as we found that women who were post-menopausal at the time of PTSD symptom assessment showed fewer symptoms than those in the other hormonal states investigated. Because of the small sample size, however, we were limited in our ability to determine if there are statistically significant differences. One possibility of these data is that because each of these women was treated for breast cancer, the lower PTSD symptoms in the

post-menopausal women could be due to the much smaller magnitude of hormonal suppression from the anti-endocrine therapies compared to the hormonal suppression that would occur in women who are pre-menopausal.

In the current sample, we hypothesized that women who were younger than 50 at the time of diagnosis would have greater PTSD and depression symptoms than women who were older than 50 at the time of diagnosis (Vin-Raviv et al., 2013), and this was not supported with statistical significance. That said, the small sample size may have influenced the statistical significance, as there is a trend in each of the measured symptoms showing the younger women to be more symptomatic than older women. This younger age association with higher symptoms is particularly evident in the avoidance symptom cluster, which may have implications on treatment-seeking behaviors. One possible explanation for these seemingly higher avoidance symptoms in women who are diagnosed at a younger age could reflect the fear of cancer recurrence or familial obligations to take care of children or parents (Hanprasertpong et al., 2017; Mosher & Danoff-Burg, 2006; Thewes et al., 2004). Another possibility is that because breast cancer often occurs in older women, with the mean age of diagnosis being 62 years old, the diagnosis may be much more shocking and disruptive in younger women (Cordova et al., 2007; DeSantis et al., 2019; Mosher & Danoff-Burg, 2006).

A diagnosis-related finding that ran contrary to our hypothesis was the stage of diagnosis. We hypothesized that women who were diagnosed with late-stage breast cancer would have more PTSD and depression symptoms than women diagnosed with early-stage breast cancer (Abbey et al., 2015; S. K. Smith et al., 2011); however, in our sample, early-stage diagnoses was associated with greater PTSD hyperarousal symptoms than late-stage diagnoses. This finding could be due to receiving less treatment and therefore having higher FCR. Another possible

explanation is that the severity of diagnosis is not entirely related to the development of PTSD in women, but rather the resilience of each woman compounded with other known risk factors makes more of a difference.

Cancer Treatment

Many of the results relating to cancer treatment do not support our hypotheses, and multiple factors likely contribute to this. A broad factor that differentiates our study from that of prior research on mental health outcomes in breast cancer survivors is the timeline. Many prior studies interview patients a few months or up to one year following treatment. In the current study, we assessed PTSD and depression symptoms an average of six years after a breast cancer diagnosis and therefore assessed very long-term effects on mental health. Based on the review of (Moyer & Salovey, 1996), we hypothesized that women who received a mastectomy would have greater PTSD and depression symptoms than women who received a lumpectomy. Yet our sample showed no significant differences between the two groups. Similarly, based on the finding of increased arousal and anxiety with radiation therapy, we hypothesized that women who received radiation would have greater PTSD and depression symptoms (Andersen et al., 1984), but in our sample, it was the women who had no radiation who had higher PTSD and depression symptoms. One potential explanation is that while patients who receive radiation had an association with lower PTSD symptoms, radiation occurs more commonly in tandem with less invasive surgeries (lumpectomies rather than mastectomies) (Obedian et al., 2000; Pozo et al., 1992). With that, it could be surgical trauma and lasting body image issues from the mastectomy that resulted in higher PTSD symptoms in women who did not receive radiation, rather than the lack of exposure to radiation therapy (Monteiro-Grillo et al., 2005; Pozo et al., 1992).

Regarding chemotherapy, we hypothesized that women who received chemotherapy would have greater PTSD and depression symptoms than women who did not receive chemotherapy (Pandey et al., 2006). In our sample, however, women who received chemotherapy had lower depression symptoms than women who did not receive chemotherapy. For example, these lower depression symptoms seen in women who receive chemotherapy may not be a function of the treatment itself, but rather the surrounding factors. For example, it could be that women who receive more cancer treatment are less fearful of cancer recurrence because they feel the side effects of their treatment are indicative of the cancer being eradicated. Another possibility is that women who receive chemotherapy are having more frequent interactions with medical and psychiatric professionals, so their depression symptoms can be addressed more easily due to having more treatment in a healthcare setting. When looking at how chemotherapy is associated with depression symptoms over time, we found that women who were diagnosed most recently and did not receive chemotherapy had greater depression symptoms, whereas recency of diagnosis had no impact among women who had chemotherapy. That said, because these graphs are for different women at different time points rather than following the same women over time, we cannot infer causational conclusions about PTSD and depression symptoms over time as a result of different cancer therapies.

Given the findings of adverse mental health outcomes following treatment with SERMs and aromatase inhibitors (Lumachi et al., 2013; Mook et al., 2005; Rocha-Cadman et al., 2012), we hypothesized that treatment with anti-endocrine therapy would be associated with greater PTSD and depression symptoms. In the current study, PTSD and depression symptoms in patients who had anti-endocrine therapy were not significantly different from those who did not have anti-endocrine therapy, but it would be worth investigating in a larger cohort of

women. Also, it should be mentioned that many other factors could confound these results, such as the stage of cancer diagnosis, other cancer treatments, or new traumatic events.

Given the hypothesized increase of PTSD and depression symptoms following both chemotherapy and anti-endocrine therapy, which are both systemic therapies, we hypothesized that women who received any type of systemic therapy with have greater PTSD and depression symptoms than women who did not. Yet when analyzing these data in terms of the larger scale of receiving systemic versus not receiving systemic therapies, we found that women who had some form of systemic therapy had lower PTSD and depression symptoms than women who did not have some form of systemic therapy. This, again, could be due to having more medical care overall or other confounding variables. Another possibility could be having more support from friends and family members.

The regression analyses combining the major treatment-related risk factors in a single model elucidated that years since diagnosis, age, and chemotherapy were each significant independent predictors of PTSD hyperarousal symptoms and that current age and chemotherapy were both significant predictors of depression symptoms. The commonality of chemotherapy in predicting both PTSD hyperarousal symptoms and depression symptoms strengthens the notion that chemotherapy has a psychological impact on women with breast cancer.

Overall, these analyses of how the treatment of breast cancer may impact PTSD and depression symptoms show that there is no evidence to support that compounding breast cancer treatment increases the risk for PTSD based on these data. However, our sample has data from many women who had breast cancer diagnosed and treated many years before our evaluation of their PTSD and depression symptoms. Because many studies evaluate PTSD and depression on a shorter timescale following a breast cancer diagnosis, this long-time horizon may indicate an

alteration of symptoms over 5-10 years following diagnosis. Although these results necessitate more research in order to draw formal conclusions, one possibility is that all of this is a measure of resilience. Perhaps it is primarily demographic and socioeconomic factors that place women at high or low risk for PTSD following traumatic events, and women who are resilient and/or low risk for PTSD at the time of diagnosis have better psychiatric outcome than women who are not resilient or who are at high-risk for PTSD. It is possible that the stress of the situation does not change much throughout treatment, but this statement would need to be analyzed. For example, it would be a worthwhile study to measure stress response both before and after diagnosis with breast cancer, as well as a few months into treatment to see how the stress of the diagnosis and treatment may change over time. Given this is a unique population of women who experience more trauma and are at much higher risk than the normal population for PTSD, it is possible that the stress and trauma of a breast cancer diagnosis and treatment are not as striking.

Inflammation: Obesity and Blood Chemistry

Given the findings of (Scott et al., 2008), we hypothesized that obesity would be associated with greater PTSD and depression symptoms. We found that obesity was linked with greater PTSD symptoms, specifically within the intrusive cluster of symptoms. These data fit our hypothesis which was based on prior literature surrounding adipose tissue and adipose-related inflammation (Cleary & Grossmann, 2009; Scott et al., 2008; Zass et al., 2017), and they suggest that obesity may exacerbate PTSD severity in women who have experienced breast cancer.

Although analyzing the blood biomarkers was largely exploratory, we hypothesized that normal levels of chloride, high levels of neutrophils, normal levels of hematocrit, low

levels of glucose, and high levels of lymphocytes would correlate with greater PTSD and depression symptoms. Our finding that blood chloride levels outside the normal range correlate with lower depression symptoms is consistent with our hypothesis and with the results from other research done on blood chemistry levels after trauma, which showed that levels of chloride outside of the normal range is more protective against PTSD than chloride levels in the normal range (Schultebraucks et al., n.d.). Chloride is a critical ion for normal brain function, and it is known in PTSD for being controlled by GABA receptors (Vasterling & Brewin, 2005). When chloride levels are outside the normal physiological range, one is said to have hyperchloremia or hypochloremia (Berend et al., 2012). Diseases and conditions related to hyperchloremia include renal failure, severe dehydration, and hypermetabolic states (Berend et al., 2012). In contrast, diseases and conditions related to hypochloremia include congestive cardiac failure, vomiting, and hyperadrenocorticism (Berend et al., 2012). As such, serum chloride level may indicate serious conditions among multiple body systems, and the specific underlying biological mechanisms that are associated with depression or PTSD symptoms remain unclear. While we also investigated the effect of blood glucose, hematocrit, lymphocytes, and neutrophils, the small sample size compounded with incomplete data in each group limited our ability to draw conclusions from our sample. Taking a blood sample near the time of breast cancer diagnosis could offer insight into if blood chemistry is associated with risk for PTSD following a breast cancer diagnosis.

Limitations

A major limitation of the current study is the small sample size. With data from only 49 African American women who mentioned breast cancer as a trauma, and fewer women with

complete breast cancer diagnosis and treatment data, many of the variables warrant further investigation. While we adjusted for this small size by calculating effect size, the data set would be improved by including more women and by measuring PTSD symptoms near the time of diagnosis with breast cancer compared to that a few months after the breast cancer diagnosis. Another limitation of these data is that each woman has had a unique amount of time pass since her date of breast cancer diagnosis, with some women having many years since diagnosis and treatment and others still being treated for breast cancer. Despite these limitations, the data shown here indicate that many factors may influence PTSD and depression symptoms in our trauma-exposed population of African American women, and more research on factors that increase the risk for certain women is warranted.

Conclusions

Overall, there are many factors encompassing breast cancer diagnosis and treatment that may influence PTSD and depression symptoms. Factors that are of particular interest for future research involve different treatment strategies, different cancer subtypes, and blood chemistry markers near the time of cancer diagnosis. Although these correlational findings do not indicate causality, it would be worthwhile to investigate the immediate fear response to a breast cancer diagnosis in women to better understand the underlying mechanism for women who end up developing PTSD compared to those who do not. It is possible that all of these factors each have a small role and that the fear response to the initial diagnosis is what best determines risk for PTSD in women with breast cancer, or perhaps it is the fear of cancer recurrence after cancer treatment is complete that best determines risk. More research that occurs close to the time of diagnosis and treatment of breast cancer would aid in better deciphering the impact of each

factor. Regardless, identifying women at high risk for PTSD and depression is of critical importance so that women can be better protected from adverse outcomes such as suicide and poor quality of life. Identifying high-risk patients early on and being able to provide treatment before symptoms progress too far is critical to provide the best mental health outcome in these patients and overall better quality of life.

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Tables and Figures

Table 1. Demographic table comparing control participants to breast cancer participants. Comparison of the means and standard deviations for age, traumatic event inventory (TEI), childhood trauma questionnaire (CTQ), the proportion of PTSD diagnoses, body mass index (BMI), and time between blood chemistry data and the trauma interview between controls and breast cancer.

	Control		Breast Cancer		Significance
	Mean	SDOM	Mean	SDOM	
Age	51.68	1.62	51.96	1.62	NS
TEI	4.79	0.42	4.79	0.42	NS
CTQ	39.58	2.50	36.22	2.30	NS
Proportion of PTSD Diagnosis	0.24	0.06	0.31	0.07	NS
BMI	33.57	1.73	33.34	1.34	NS
Time between blood and interview (months)	6.06	1.43	2.50	0.36	p=0.02

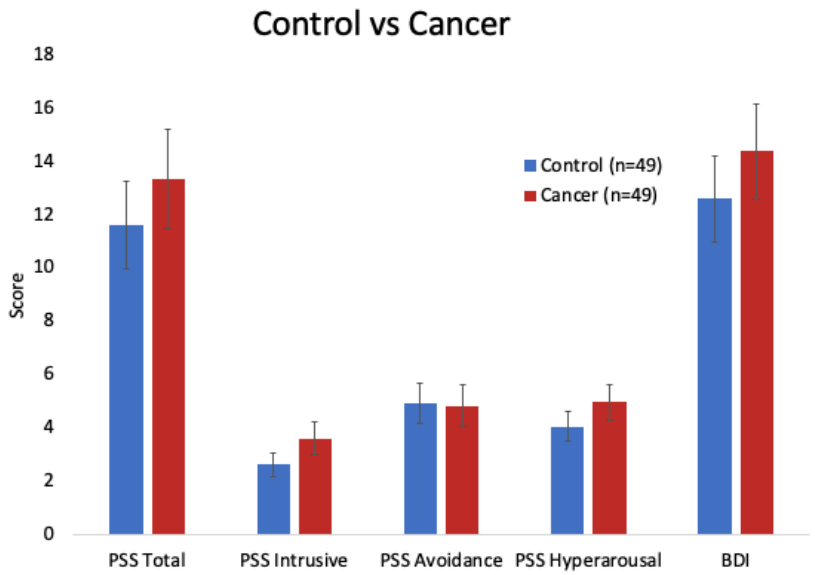

Figure 1. PTSD and depression symptoms in women who had breast cancer compared to age- and trauma-matched controls. When comparing women with breast cancer to age- and trauma-matched controls, there were no significant differences in total PSS, PSS intrusive, PSS avoidance, PSS hyperarousal, or BDI scores, $p > 0.05$.

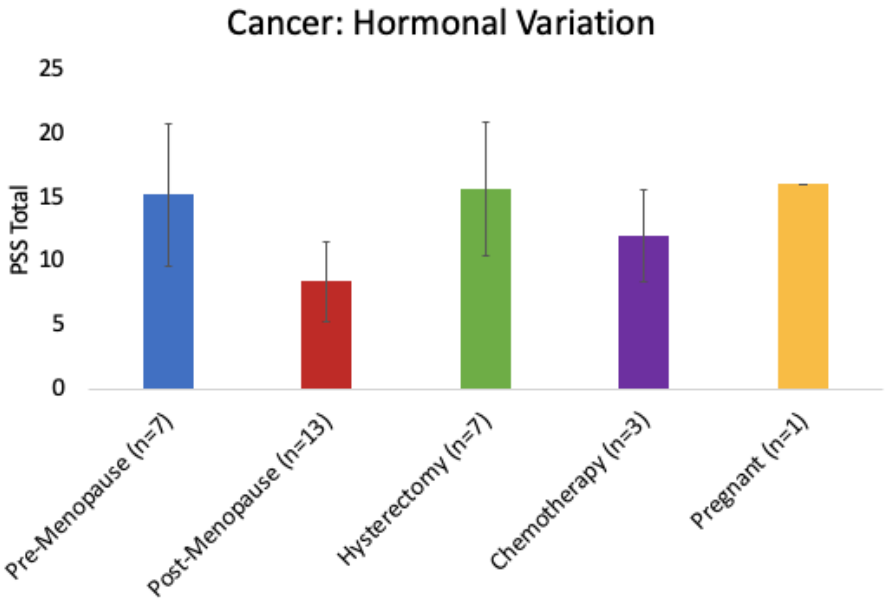

Figure 2. PTSD total in women at varying hormonal states. Women who were pre-menopausal, post-menopausal, had a hysterectomy, not cycling due to chemotherapy, or pregnant were compared. While the pre-menopausal group appears to show greater PSS scores than the post-menopausal group, there are no significant differences, $p > 0.05$.

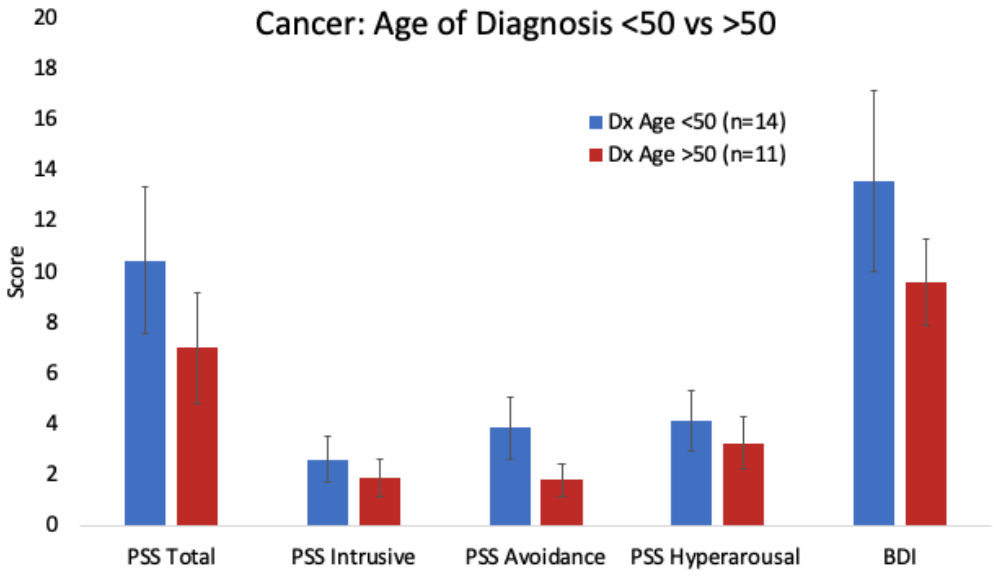

Figure 3. PTSD and depression symptoms in women who were <50 versus >50 years old at the time of their breast cancer diagnosis. Women who were <50 at the time of diagnosis had no significant differences in PSS total, PSS intrusive, PSS avoidance, or BDI scores from women >50 at the time of diagnosis, $p > 0.05$.

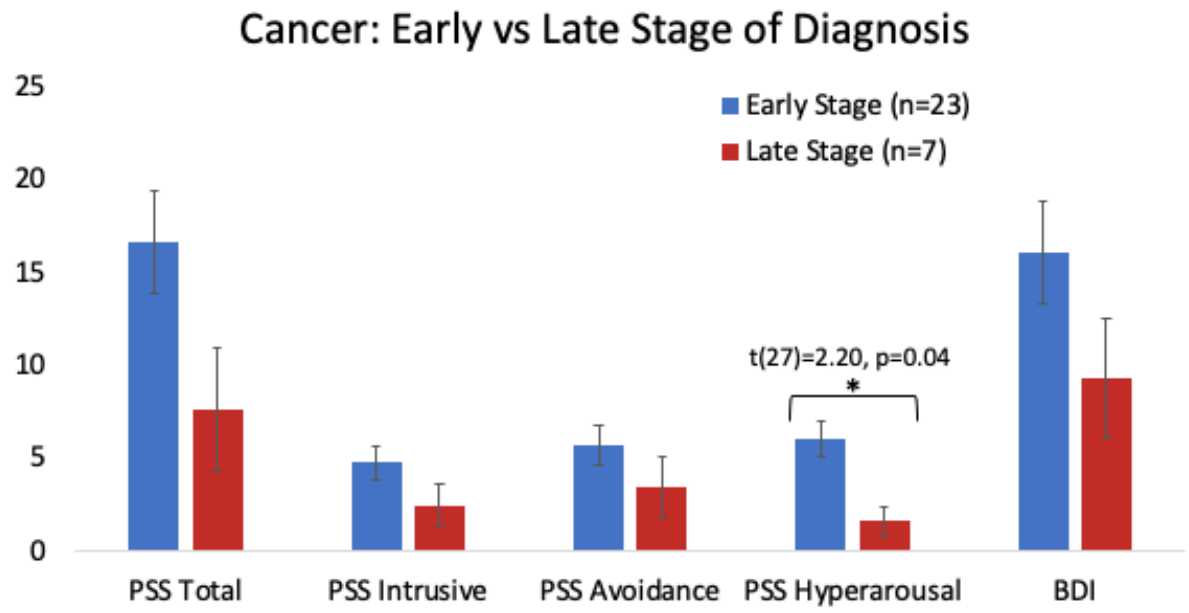

Figure 4. PTSD and depression symptoms in women who were diagnosed with early- or late-stage breast cancer. Of the women who had breast cancer, those who had early-stage breast cancer had higher PSS hyperarousal scores. There was no significant difference in PSS total, PSS intrusive, PSS avoidance, or BDI scores, $p > 0.05$.

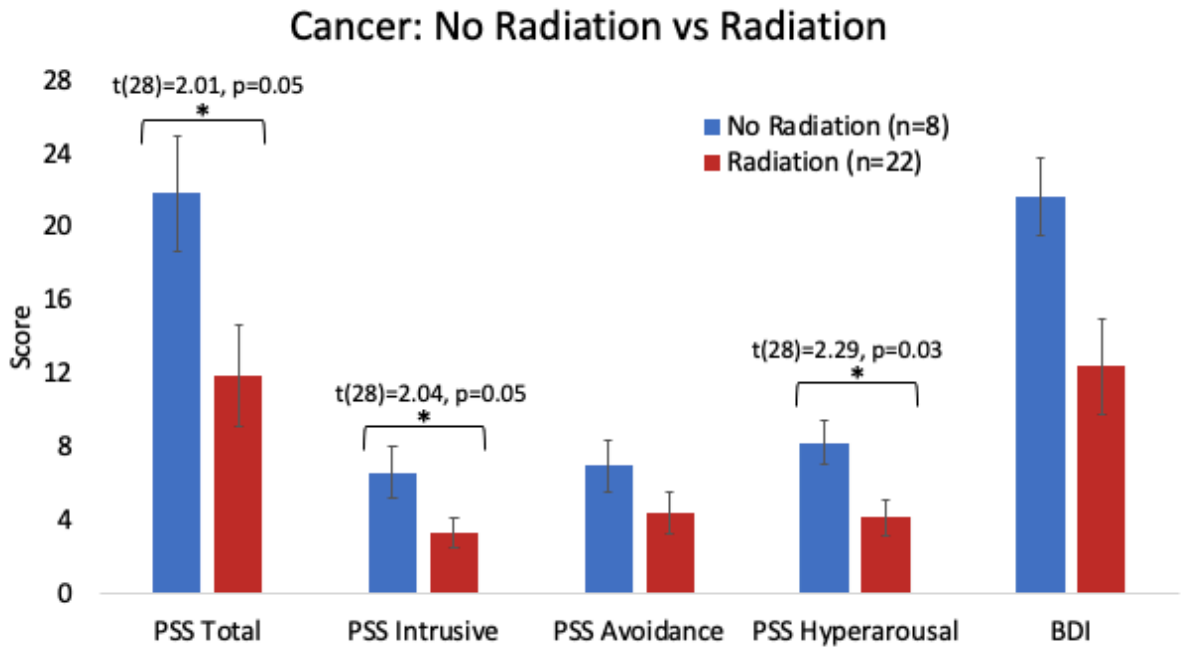

Figure 5. PTSD and depression symptoms in women who did or did not receive radiation therapy. Women who received radiation had lower PSS total, PSS intrusive, and PSS hyperarousal scores. There was no significant difference in PSS avoidance or BDI scores based on radiation, $p > 0.05$.

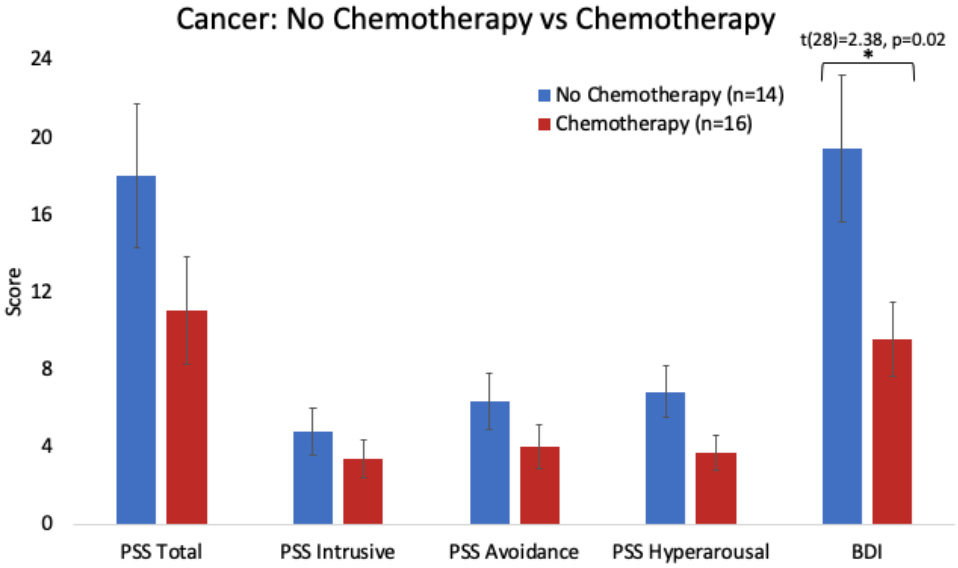

Figure 6. PTSD and depression symptoms in women who did or did not receive chemotherapy. Women who received chemotherapy had lower BDI scores than women who did not receive chemotherapy. There were no significant differences in PSS total, PSS intrusive, PSS avoidance, or PSS hyperarousal, $p > 0.05$.

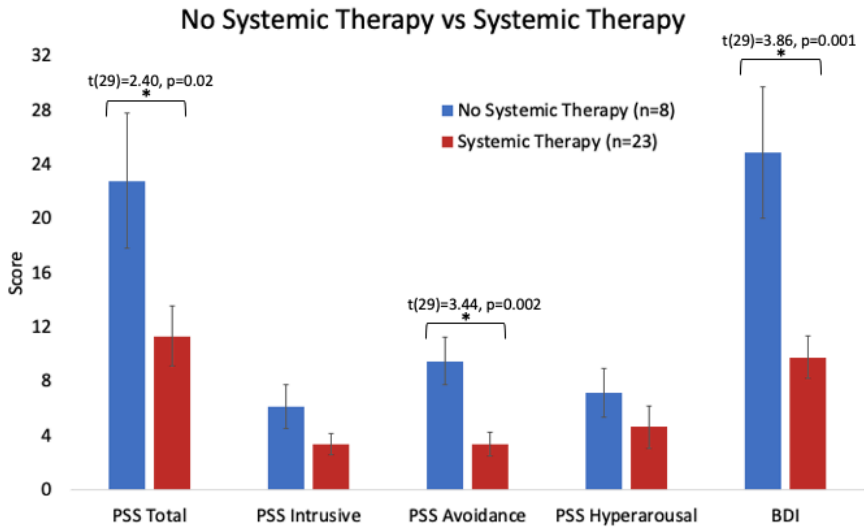

Figure 7. PTSD and depression symptoms in women who did or did not receive systemic therapy. Women who received one or more forms of systemic therapy had higher PSS total, PSS avoidance, and BDI scores than women who did not. There were no significant differences in PSS intrusive or PSS hyperarousal scores, $p > 0.05$.

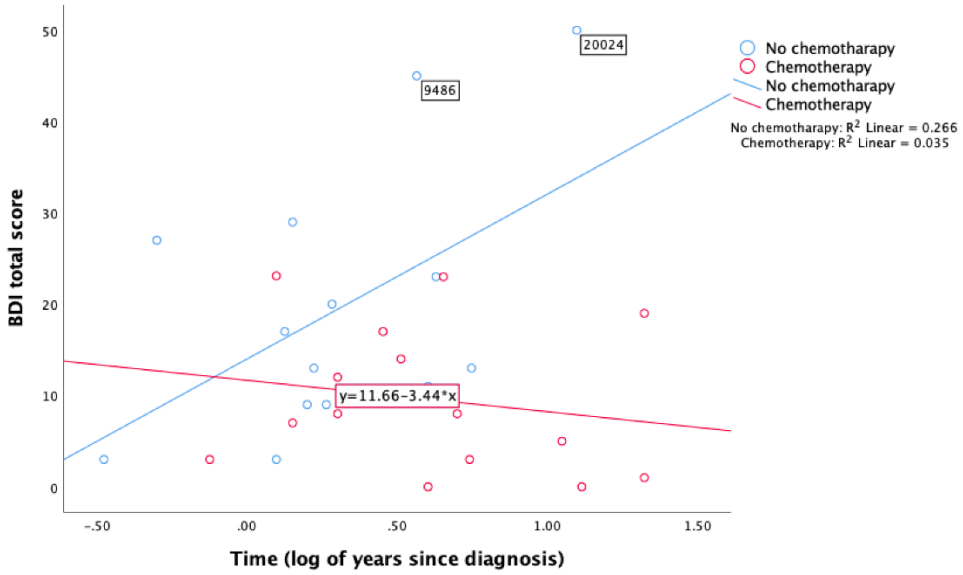

Figure 8. BDI total score as a function of time in log years since diagnosis in women who did and did not receive chemotherapy. Women who did not receive chemotherapy have a positive slope for BDI score over time ($R^2 = 0.27$), whereas women who received chemotherapy have a negative slope for BDI score over time with a very small correlation ($R^2 = 0.04$).

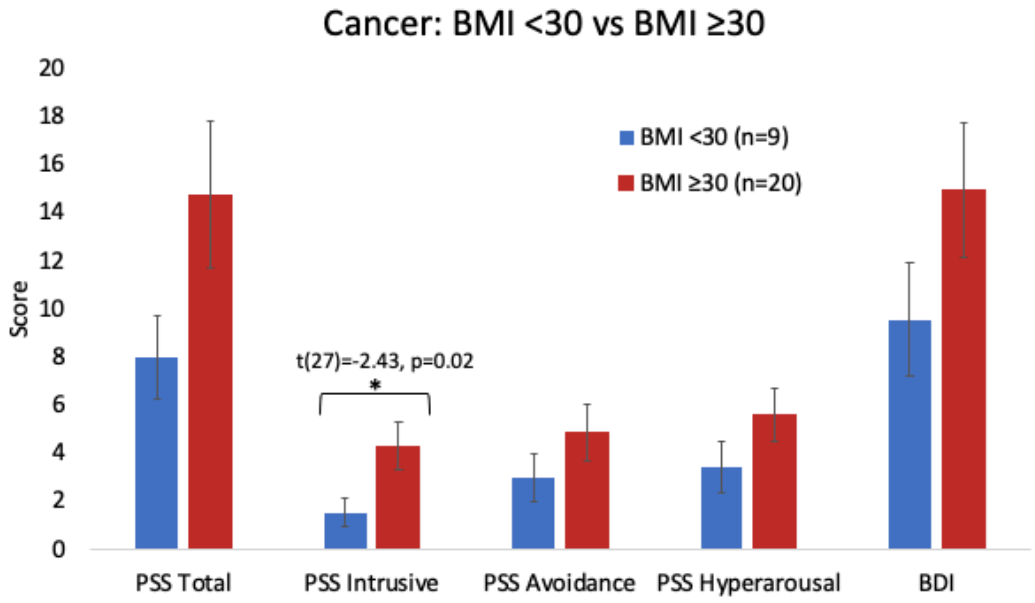

Figure 9. PTSD and depression symptoms in women with a breast cancer diagnosis who have a BMI <30 compared to a BMI ≥30. Of the women who had breast cancer, those who had a BMI ≥30 had higher PSS intrusive scores. There was no significant difference in PSS total, PSS avoidance, PSS hyperarousal, or BDI scores, $p > 0.05$.

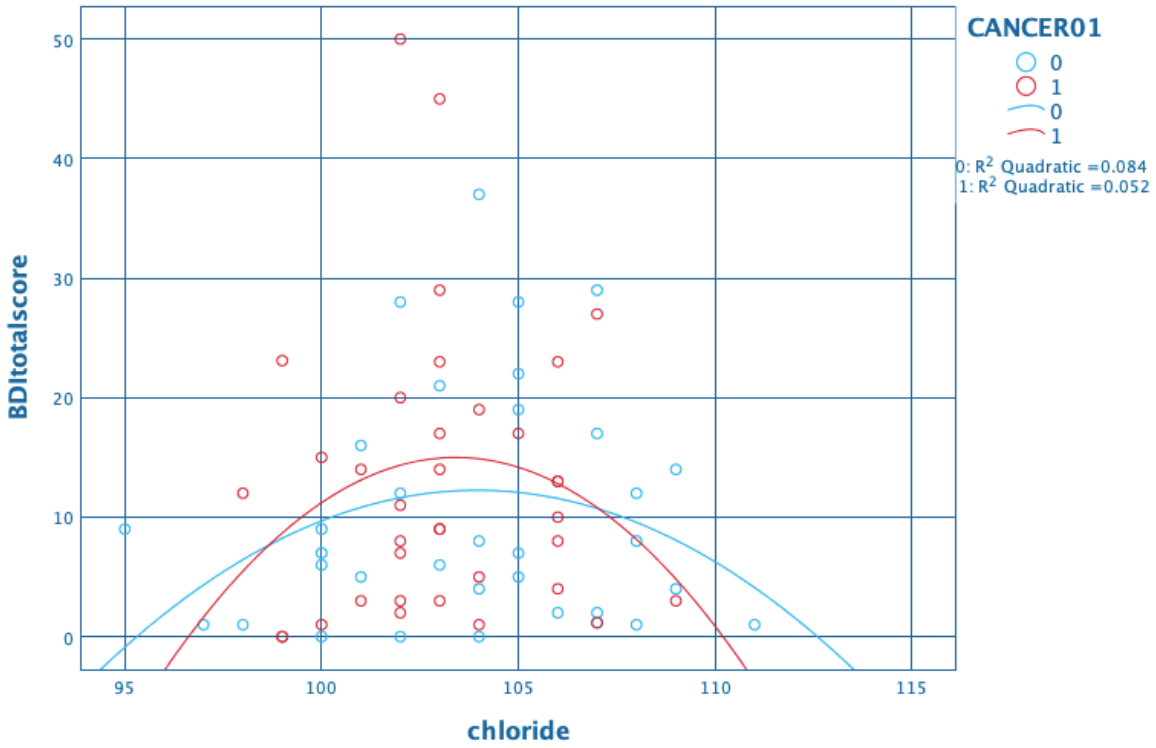

Figure 10. Quadradic curves of BDI as a function of chloride levels. Irrespective of cancer diagnosis, normal biological levels of chloride correlate with higher BDI scores than abnormal chloride levels.