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Chronic and episodic stress predict physical symptom bother following breast cancer diagnosis

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Abstract Breast cancer patients often experience adverse physical side effects of medical treatments. According to the biobehavioral model of cancer stress and disease, life stress during diagnosis and treatment may negatively influence the trajectory of women's physical health-related adjustment to breast cancer. This longitudinal study examined chronic and episodic stress as predictors of bothersome physical symptoms during the year after breast cancer diagnosis. Women diagnosed with breast cancer in the previous 4 months ($N = 460$) completed a life stress interview for contextual assessment of chronic and episodic stress severity at study entry and 9 months later. Physical symptom bother (e.g., pain, fatigue) was measured at study entry, every 6 weeks through 6 months, and at nine and 12 months. In multilevel structural equation modeling (MSEM) analyses, both chronic stress and episodic stress occurring shortly after diagnosis predicted greater physical symptom bother over the study period. Episodic stress reported to have occurred prior to diagnosis did not predict symptom bother in MSEM analyses, and the interaction between chronic and episodic stress on symptom bother was not significant. Results suggest that ongoing chronic stress and episodic stress occurring shortly after breast cancer diagnosis are important predictors of bothersome symptoms during and after cancer treatment. Screening for chronic stress and recent stressful life events in the months following diagnosis may help to identify breast cancer patients at risk for persistent and bothersome physical symptoms. Interventions to prevent or ameliorate treatment-related physical symptoms may confer added benefit by addressing ongoing non-cancer-related stress in women's lives.

Keywords Stress · Life events · Breast cancer · Physical symptoms · Survivorship

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Introduction

Women with breast cancer typically undergo intensive medical treatments, which can include surgery, radiation therapy, chemotherapy, hormonal therapy, and/or biologic therapy. These treatments often cause adverse physical side effects such as fatigue, pain, and nausea (e.g., Bower, 2008; Shapiro & Recht, 2001). Although most women with breast cancer adjust well physically and psychologically over the long term (Ganz et al., 2011), some experience substantial and long-lasting physical symptoms that interfere with daily functioning and quality of life (Bower, 2008; Helgeson et al., 2004). Nearly two-thirds of women with breast cancer report post-surgical pain (Davies, 2013), and between 30 and 100% experience sexual difficulties (DeSimone et al., 2014). One-fourth of breast cancer patients experience significant fatigue for years after treatment (Bower, 2014). Women who report greater cancer-related physical symptoms during treatment are at higher risk for later cancer-related distress, intrusive thoughts, and general distress (Jim et al., 2007). Given the high prevalence and persistence of physical symptoms experienced by women with breast cancer and their long-term implications for health and well-being, early identification of key predictors of bothersome physical symptoms is crucial in order to target at-risk women for prevention and timely intervention. Prospective research investigating psychosocial predictors of bothersome physical symptoms associated with breast cancer, however, is limited. The current study examined contextually-rated chronic and episodic life stress occurring prior to and shortly after diagnosis as early risk factors for persistent physical symptoms during the year after breast cancer diagnosis.

In addition to facing a diagnosis of breast cancer, women often experience ongoing, chronic stress in other life domains (e.g., financial insecurity, relationship problems; Vickberg, 2003) as well as stressful life events unrelated to their cancer diagnosis or treatment (e.g., death or illness of a loved one; Golden-Kreutz & Andersen, 2004). Adjustment to a prominent stressor such as breast cancer is best understood in the context in which it occurs (Revenson, 2003) and according to the biobehavioral model of cancer stress and disease (Andersen et al., 1994; Lutgendorf & Andersen, 2015), life stress during the process of cancer diagnosis and treatment can contribute to deterioration in quality of life. Consistent with this model, empirical evidence demonstrates that non-cancer-related stressful life events (Burgess et al., 2005; Golden-Kreutz & Andersen, 2004; Golden-Kreutz et al., 2005; Grassi et al., 1997; Kornblith et al., 2001) and perceived overall stress (Golden-Kreutz & Andersen, 2004; Golden-Kreutz et al., 2005) are significant predictors of poorer psychological adjustment to breast cancer. In one longitudinal study, however, stressful life events did not predict change in psychological adjustment (i.e., depressive symptoms, cancer-specific distress, vitality, perceived personal growth) during the year after breast cancer treatment completion (Low et al., 2006). Notably, with the exception of Burgess et al. (2005), the above studies employed subjective ratings of perceived overall stress and/or checklist measures to assess stressful life events despite research suggesting that interview-based contextual (i.e., based on objective features of the stress given the context in which it occurs) measurement of severity of threat from acute life events and ongoing difficulties more effectively predicts outcomes, facilitates more accurate recall of events, and is less subject to participant bias based on current mood (Hammen, 2005).

Furthermore, research examining life stress as a predictor of bothersome physical symptoms in breast cancer is limited. A longitudinal study of women who had recently undergone breast cancer surgery found that perceived overall stress, perceived cancer-related stress, and stressful life events reported on a checklist measure as occurring during the year prior to diagnosis predicted poorer physical quality of life during adjuvant treatment and after treatment completion (Golden-Kreutz et al., 2005). The current study expands upon previous research by prospectively examining the relationships between contextually-rated chronic stress (i.e., ongoing, taxing experiences) and episodic stress (i.e., discrete life events that are likely to tax or exceed personal resources) and bothersome physical symptoms during the year after breast cancer diagnosis. Henceforth, "stress" in this report refers to the context-based severity of stressful life events (episodic) and difficulties (chronic).

If stress occurring within the first months after diagnosis predicts bothersome symptoms months later, careful interpretation of this finding is warranted. Specifically, it is useful to ask whether early stress has an enduring impact or whether women who experience heightened stress shortly after diagnosis continue to experience heightened stress during and after treatment, which could then contemporaneously affect physical symptoms. As a secondary aim, the current study examined this question by assessing correlations between stress ratings at study entry (within 4 months of diagnosis) and 9 months later (approximately 1 year after diagnosis).

Hypotheses were that higher levels of both chronic and episodic stress, compared with lower stress, would predict greater and more persistent physical symptom bother over time, and that proximal episodic stress, occurring in the first months following breast cancer diagnosis, would have a stronger relation to symptom bother than episodic stress

reported to have occurred in the months prior to diagnosis. Furthermore, chronic stress was expected to be a stronger predictor of persistent symptom bother than episodic stress, because the latter is more likely to resolve (Diener et al., 2006). Accordingly, chronic stress at study entry was expected to be highly correlated with chronic stress 1 year after diagnosis, whereas episodic stress at study entry was expected to be weakly correlated with episodic stress 1 year post-diagnosis. Finally, an interaction between chronic and episodic stress was predicted such that high levels of episodic stress in the context of high chronic stress would predict particularly high symptom bother, reflecting a cumulative effect (Brown & Harris, 1978).

Method

Participants

The current study involves secondary analysis of data from a longitudinal study examining psychosocial and cancer-related predictors of depression and other outcomes among recently diagnosed breast cancer patients (Bauer et al., 2016; Marroquín et al., 2016; Stanton et al., 2015). Of 823 women approached to participate, 61 were ineligible (8%). Of the 762 eligible women, 302 (40%) declined to participate or were unreachable by telephone, and 460 (60%) consented and completed an initial in-person assessment within 4 months of breast cancer diagnosis. Participants completed telephone assessments every 6 weeks through 6 months after the initial assessment, another in-person assessment at 9 months, and a telephone assessment at 12 months. Overall attrition was 19% at study end (Stanton et al., 2015).

Procedure

The relevant Institutional Review Boards approved all study procedures. Women were recruited from oncology clinics in the greater Los Angeles, California area and in Tucson, Arizona. Within scheduling constraints, consecutive newly diagnosed or newly recurrent breast cancer patients were informed of the study by clinic or research staff following a standard verbal script. With verbal consent, study personnel contacted interested women to provide information and screen for eligibility: (1) new or recurrent diagnosis of invasive breast cancer within 4 months prior to the initial assessment, (2) at least 21 years of age, and (3) ability to complete assessments in English. Any standard medical treatment for cancer (i.e., surgery, chemotherapy, radiotherapy, neoadjuvant chemotherapy, endocrine therapy) and any additional medications were allowed. Exclusion criteria were current or past bipolar disorder, schizophrenia, schizoaffective disorder, or cognitive disorder (e.g., dementia), and current suicidality.

The initial assessment, conducted by trained post-baccalaureate level research staff, required 3 h and was completed in a private room at the treating oncology center or at women's homes. After giving informed consent, participants completed self-report measures and a semi-structured interview. Women began by completing self-report measures in interview format and were given the option to complete the remaining items independently on the computer with the interviewer present.

During follow-up telephone assessments, which lasted approximately 30 min each, participants responded verbally to items. The in-person assessment at 9 months was conducted in a similar fashion to the initial assessment and required approximately 2 h. Women were compensated $60 for in-person assessments and $30 for telephone assessments.

Measures

Demographic and cancer-related variables

Age, marital status, ethnicity, household income, education, employment, subjective social status (Kilpatrick & Cantril, 1960), body mass index, and number of comorbid physical diseases (Groll et al., 2005) were collected by self-report at study entry. Cancer-related variables (cancer stage, chemotherapy, surgery, radiation therapy, herceptin use, endocrine therapy use) were reported at study entry and each subsequent assessment. Cancer stage was obtained through medical chart review; self-reported cancer stage was used when the chart was unavailable ($n = 39$).

Stress

The UCLA Life Stress Interview (LSI; Hammen, 1991a) was administered at study entry and 9 months to assess contextual severity of chronic and episodic life stress. The LSI is a psychometrically reliable and well-validated semi-structured interview to evaluate stressful life events, as well as chronic stress in nine life domains (i.e., close friendships, romantic relationships, family of origin, children, finances, work, academics, health of self, health of family; Hammen et al., 2009; Daley et al., 2000). The "health of self" domain did not include assessment of cancer-related content. At study entry, chronic and episodic stress were retrospectively reported for the 6 months prior to breast cancer diagnosis (pre-diagnosis) and from diagnosis to study entry (post-diagnosis). At 9 months, chronic and episodic stress since study entry were assessed.

Chronic stress As per protocol (Hammen, 1991b), interviewers assessed chronic stress by querying typical conditions in each life domain and then rating each domain on a five-point scale in increments of .5, ranging from 1 (*exceptionally positive circumstances*) to 5 (*extremely adverse circumstances*) and using descriptive behavioral anchors. For example, for the domain of romantic relationships, a score of 2 represents a stable, positive relationship (close, confiding, trusting), and 4 represents a deteriorating relationship or severe problems in the relationship (unstable, poor conflict resolution). Study entry chronic stress ratings were averaged across all domains to yield a total chronic stress score (Hammen et al., 2009). Previous research has demonstrated the stability of LSI chronic stress ratings (e.g., Daley et al., 2000). Because study entry chronic stress ratings for pre- and post-diagnosis were highly correlated ($r = .92$, $p < .001$), they were averaged and the overall chronic stress rating was used for the initial score, with higher ratings indicating more chronic stress. A separate score was calculated for total chronic stress at 9 months.

Episodic stress Participants were asked in the study entry interview whether "any particular events had occurred" in the 6 months prior to breast cancer diagnosis (pre-diagnosis) or since diagnosis (post-diagnosis) in each of the nine domains, as well as whether any other events not captured by the queried domains (e.g., auto accident) had occurred during the same time periods. At 9 months, participants were asked about events that had occurred since study entry. Interviewers provided examples of events in each domain. For instance, interviewers asked whether any major arguments had occurred when assessing episodic stressors in interpersonal domains. Interviewers gathered details about the context in which each reported event occurred (e.g., what happened, consequences, controllability) in order to assess the severity of the event given its unique features for that individual's life. Normative cancer-related events (e.g., surgery, change in treatment plan) were not included.

Interviewers then presented each event in narrative form to a coding team of at least two trained post-baccalaureate level research staff who were blind to the participant's reactions to events. The team, excluding the interviewer, rated the impact of each event on a severity scale ranging from 1 (*none*) to 5 (*extremely severe*) in increments of .5 based on the severity of impact on the life course of a typical individual under identical circumstances. Ratings were reached by consensus. Separate study entry episodic stress ratings for pre- and post-diagnosis were calculated by summing the impact ratings of all events with at least moderate impact or higher, scored at 2 or above (Hammen et al., 2009; Rudolph et al., 2000). Separate study entry pre- and post-diagnosis ratings were retained for separate analyses because they were not significantly correlated. A third score was calculated for episodic stress at 9 months. Higher ratings indicate higher severity and/or more frequent occurrence of episodic stressors.

Physical symptom bother

Measured at each assessment, bother from physical symptoms was assessed using the 25-item Breast Cancer Prevention Trial Symptom Scales (BCPT; Stanton et al., 2005). This measure was developed specifically to assess bother from common cancer and treatment-related side effects and symptoms among women diagnosed with breast cancer. Previous studies have established that the BCPT has discriminant validity, as evidenced by modest negative correlations with health-related quality of life, and is distinct from mood (Cella et al., 2008). Although the BCPT was correlated with depressive symptoms ($r = .43$, $p < .05$), only the cognitive symptom subscale was significantly correlated with depression ($r = .46$, $p < .05$). Due to the prevalence and impact of fatigue and sexual problems among breast cancer patients (Bower, 2014; DeSimone et al., 2014), the BCPT was expanded to include four items for those problems, for a total of 10 subscales (i.e., hot flashes, nausea, bladder control, pain, cognitive problems, weight problems, arm problems, vaginal symptoms, fatigue, sexual problems). Respondents indicated how much they had been bothered by each symptom during the past 4 weeks on a scale ranging from 0 (*not at all*) to 4 (*extremely*). The mean score on the expanded BCPT (average of all items) was used; higher scores indicate greater symptom bother. Internal consistency reliability was high at all assessments ($\alpha = .83$ to $.87$).

Data analysis

Descriptive statistics were calculated for all study variables. Pearson correlation coefficients between predictors (study entry chronic stress, episodic stress pre- and post-diagnosis) and the outcome variable (BCPT) at each assessment were calculated. Correlations between stress variables at study entry and 9 months were calculated to examine stability of stress ratings over time.

Due to the hierarchical nature of the data, with repeated assessments (Level 1) nested within participants (Level 2), multilevel structural equation modeling (MSEM; du Toit & du Toit, 2008; Muthén & Muthén, 2012) was conducted in Mplus version 7.3. MSEM allows for testing effects of time-varying (measured at multiple time points) and time-invariant (measured at one time point) predictors on a time-

varying outcome. The growth models included a random intercept to characterize variability between participants in symptom bother at study entry, as well as random linear and quadratic terms. Models were estimated using full information maximum likelihood (Enders & Bandalos, 2001), which includes cases with missing data on predictors. Missingness on predictors was minimal (3.9% for all predictors). Two-tailed significance tests were used throughout.

An unconditional model without predictors or covariates was estimated to examine the overall symptom trajectory over the study period. To test random intercept, linear and quadratic terms, likelihood ratio tests (Hayes, 2006) were conducted. All significant variance and covariance components were retained in subsequent models.

Covariates were selected using a combined theoretical and empirical approach (see Bauer et al., 2016). First, potential covariates were selected based on their theoretical relationship with the outcome. Then, MSEM was used to examine the univariate relation of each sociodemographic (age, marital status, ethnicity, household income, education, employment status, subjective social status, body mass index, comorbidities, recruitment site) and cancer-related (cancer stage, chemotherapy, surgery, radiation therapy, herceptin use, endocrine therapy use, study assessment at which last medical treatment occurred) covariate with the trajectory of symptom bother over time. Quadratic and linear time interactions were tested with each variable and dropped if not significant ($p > .05$). All variables that were significantly related to the outcome were retained as covariates in subsequent models, along with any significant higher-order terms. Finally, we tested a multivariate model including all potential covariates to identify variables that were non-significant in univariate analyses but emerged as significant when examined with other variables. Variables and higher-order terms that emerged as newly significant in multivariate analyses were added to the final covariate model.

Time was centered at the average number of months since diagnosis at study entry ($M = 2.13$). Time-varying treatment status variables (e.g., chemotherapy) were analyzed as Level 1 variables. Study entry chronic and episodic stress and other time-invariant variables measured at study entry only (e.g., income) were analyzed as Level 2 variables.

To examine main effects of study entry chronic stress, pre-diagnosis episodic stress, and post-diagnosis episodic stress on symptom bother over time, stress variables with quadratic and linear time interactions were tested in separate models containing covariates. Non-significant higher-order terms were dropped from the models one by one. Chronic stress at study entry and pre-diagnosis episodic stress, as well as chronic stress at study entry and post-diagnosis episodic stress, were also examined in the same models to evaluate the unique predictive utility of each type of stress. Moderation models with interactions between chronic and episodic stress variables (as well as their quadratic and linear effects with time) were tested; episodic stress occurring prior to diagnosis and episodic stress occurring shortly after diagnosis were tested separately with study entry chronic stress. All predictor variables were centered at the grand mean of each respective variable. Effect sizes were calculated using proportion of Level 2 intercept variance, an analog of R^2.

Results

Participant characteristics

Women were on average 56 years old ($SD = 12.6$ years; range 23–91 years). Over half (55%) had graduated from a 4-year college, 20% had some college education, 21% had a high school education, and 4% did not graduate from high school. About one-third (29%) had an annual household income under $50,000, and another third (36%) had an income over $100,000. Most (68%) were non-Latina white, and a substantial minority (19%) were Latina. Approximately half (52%) were employed, 30% were retired, and 18% were unemployed. Two-thirds (67%) were married. On average, women reported 1.8 ($SD = 1.9$) physical comorbidities. See Stanton et al. (2015) for additional details regarding participant characteristics.

Initial assessments occurred, on average, 2.13 months after women's breast cancer diagnosis ($SD = .81$; see Table 1). The majority were diagnosed with Stage 1 (43%) or Stage 2 (39%) cancer. At study entry, 60% had undergone surgery within the past 6 weeks, and 42% were on chemotherapy or had completed chemotherapy within the past 6 weeks.

Descriptive statistics

Means and correlations between study variables are displayed in Tables 2 and 3. Chronic stress ratings indicated that women experienced, on average, mild to moderate chronic stress across domains at both study entry and 9 months. During the 6 months prior to diagnosis, 42% of women reported experiencing a significant episodic stressor; 21% reported a significant episodic stressor in the approximately 2 months between diagnosis and study entry, and 49% reported a significant episodic stressor from study entry to 9 months.

Chronic stress in the previous $8 \pm .8$ months (study entry) was significantly but weakly correlated with episo-

Table 1 Cancer- and treatment-related variables (N = 460)

Variable	Study entry *M* (*SD*)/*n* (%)	6 weeks *M* (*SD*)/*n* (%)	12 weeks *M* (*SD*)/*n* (%)	18 weeks *M* (*SD*)/*n* (%)	24 weeks *M* (*SD*)/*n* (%)	9 months *M* (*SD*)/*n* (%)	12 months *M* (*SD*)/*n* (%)
Months since diagnosis	2.13 (.8)	3.79 (1.0)	5.21 (1.1)	6.54 (1.0)	7.99 (1.0)	11.47 (1.0)	14.6 (1.0)
Stage							
1	197 (43.8)						
2	176 (39.1)						
3	52 (11.6)						
4	25 (5.6)						
Chemotherapy in past 6 weeks	183 (41.7)	167 (42.3)	110 (28.4)	53 (13.8)	27 (7.0)	11 (2.8)	5 (1.4)
Radiation therapy in past 6 weeks	31 (7.0)	35 (8.9)	19 (4.5)	44 (11.5)	39 (10.1)	13 (3.4)	2 (.5)
Surgery in past 6 weeks	270 (59.6)	57 (14.4)	43 (11.1)	59 (15.4)	48 (12.5)	47 (12.1)	30 (8.2)
Taking estrogen antagonist	30 (6.6)	45 (11.5)	53 (13.8)	67 (17.5)	85 (22.1)	124 (32.1)	110 (30.1)
Taking aromatase inhibitor	37 (8.2)	64 (16.3)	71 (18.4)	75 (19.6)	79 (20.6)	108 (28.0)	112 (30.7)
Taking herceptin	72 (15.9)	75 (19.1)	80 (20.7)	82 (21.4)	79 (20.5)	82 (21.2)	42 (11.4)
Completed treatment since most recent assessment	112 (24.5)	54 (11.8)	48 (10.5)	75 (16.4)	85 (18.6)	47 (10.3)	36 (7.9)

Table 2 Correlations between major variables at each assessment point

Variable	*M* (*SD*)	2	3	4	5	6	7	8	9	10
1. Study entry chronic stress	2.25 (.39)	.16**	.14**	.25***	.29***	.35***	.31***	.34***	.34***	.37***
2. Pre-diagnosis episodic stress	1.43 (2.07)	–	.08	.16**	.12*	.15**	.11*	.09	.16**	.12*
3. Post-diagnosis episodic stress	.63 (1.35)		–	.21***	.24***	.22***	.11*	.19***	.20***	.24***
4. Study entry BCPT	.83 (.50)			–	.71***	.69***	.63***	.58***	.61***	.57***
5. 6-week BCPT	.80 (.46)				–	.77***	.72***	.63***	.65***	.59***
6. 12-week BCPT	.85 (.50)					–	.80***	.73***	.67***	.63***
7. 18-week BCPT	.79 (.48)						–	.80***	.67***	.63***
8. 24-week BCPT	.76 (.48)							–	.73***	.72***
9. 9-month BCPT	.71 (.49)								–	.81***
10. 12-month BCPT	.67 (.47)									–

BCPT Breast Cancer Prevention Trial Symptom Scale

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 3 Correlations between stress variables at study entry and 9 months

Variable	*M* (*SD*)	2	3	4	5
1. Study entry chronic stress	2.25 (.39)	.16**	.14**	.92***	.13**
2. Pre-diagnosis episodic stress	1.43 (2.07)	–	.08	.16**	.17**
3. Post-diagnosis episodic stress	.63 (1.35)		–	.17**	.32***
4. 9-month chronic stress	2.28 (.40)			–	.21***
5. 9-month episodic stress	1.88 (2.50)				–

* $p < .05$, ** $p < .01$, *** $p < .001$

dic stress prior to diagnosis ($r = .16$, $p < .01$) and with episodic stress between diagnosis and study entry ($r = .14$, $p < .01$). Chronic stress at study entry was moderately correlated with symptom bother throughout the study period (range: $r = .25$–$.37$, all $ps < .001$). Episodic stress pre-diagnosis was not significantly related to episodic stress shortly after diagnosis, and was significantly but weakly correlated with symptom bother at nearly all assessments (range: $r = .11$–$.16$, all $ps < .05$, except $p = .07$ at 24 weeks). Episodic stress shortly after diagnosis was significantly related to symptom bother at all assessments (range: $r = .11$–$.24$, all $ps < .05$).

Chronic stress ratings at study entry and the 9-month assessment were highly correlated ($r = .92$, $p < .001$). There was a small but significant correlation between episodic stress pre-diagnosis and at 9 months ($r = .17$, $p < .01$) and a moderate correlation between episodic stress shortly after diagnosis and at 9 months ($r = .32$, $p < .001$).

Overall physical symptom trajectory

In the 12 months following study entry, on average, the overall symptom trajectory (see Fig. 1) remained constant during the first few months (linear: $b = -.06, p = .07$) and decreased thereafter (quadratic: $b = -.34$, $p < .001$). Deviance change tests revealed significantly better model fit when random intercept (χ^2 (1) = 45.95, $p < .001$), random linear (χ^2 (2) = 785.19, $p < .001$), and random quadratic (χ^2 (3) = 26.16, $p < .001$) terms were included, indicating significant differences in intercepts, linear trends, and quadratic trends across women.

Covariates

When MSEM models were used to test the univariate effects of each potential covariate on symptom bother, no significant relationships emerged for ethnicity, education, body mass index, perceived social status, physical comorbidities, or surgery. Compared with employment, unemployment and retirement were each associated with higher symptom bother across time ($b = .24$, $p < .001$ and $b = .06$, $p < .001$, respectively), as was more advanced cancer stage ($b = .05$, $p < .05$). Linear and quadratic time trends for these variables were nonsignificant.

Age, marital status, income, radiation, herceptin use, and assessment at which last treatment occurred were related to the linear, but not the quadratic, time trend. Younger age was associated with greater symptom bother at study entry, and the effect became larger over time (intercept: $b = -.01$, $p < .001$, linear: $b = .01$, $p < .01$). Married women, women with higher incomes, women prescribed herceptin, and women who completed oncologic treatment later reported higher symptom bother at study entry, and the effect became smaller over time (intercept: $b = .14$, $p < .01$, linear: $b = -.14$, $p < .01$ for marital status; intercept: $b = .08$, $p < .001$, linear: $b = -.06$, $p < .01$ for income; intercept: $b = .13$, $p < .01$, linear: $b = -.16$, $p < .05$ for herceptin; intercept: $b = .07$, $p < .001$, linear: $b = -.02$, $p < .05$ for later treatment completion). Radiation was related to less symptom bother at study entry, and the effect became larger over time (intercept: $b = -.11$, $p < .01$, linear: $b = .18$, $p < .05$).

Study site, chemotherapy, and endocrine therapy predicted the quadratic time trajectory. Participants in California reported greater symptom bother at study entry, and the effect decreased more quickly than for those in Arizona and leveled off (intercept: $b = .28$, $p < .001$, linear: $b = -.27$, $p < .05$, quadratic: $b = .32$, $p < .01$). Chemotherapy was not related to symptom bother at study entry, but linear and quadratic time trends were significant (linear: $b = .34$, $p < .05$, quadratic: $b = -.49$, $p < .05$). Endocrine therapy was not related to the intercept or linear time trend, but the quadratic time trend was significant ($b = .19$, $p < .05$).

Next, a multivariate model was tested. In the multivariate model, ethnicity did not significantly predict the intercept or linear time trend, but Latina ethnicity was related to an increasing escalation in symptom bother over time (quadratic: $b = .33$, $p < .05$). Number of comorbidities was associated with greater symptom bother at study entry ($b = .06$, $p < .001$); linear and quadratic time trends were not significant. Ethnicity (with quadratic and linear time trends) and comorbidities were added to the final covariate model. Education, perceived social status, body mass index, and surgery remained nonsignificant in multivariate analyses and were not included in subsequent models. See Table 4 for all variables included in the final model.

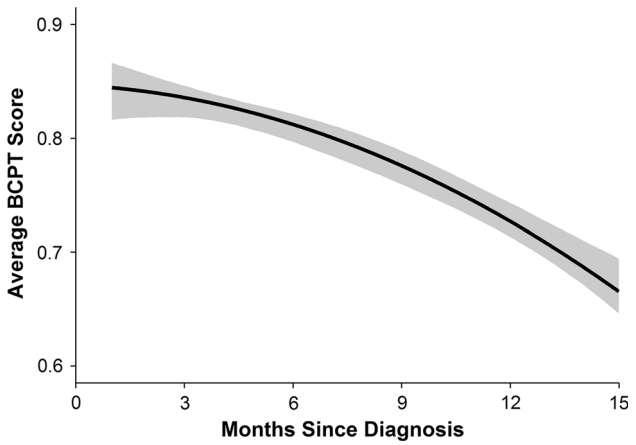

Fig. 1 Overall mean symptom trajectory for Breast Cancer Prevention Trial Symptom Scale

Effects of chronic and episodic stress on physical symptom bother

Study entry chronic stress predicted the BCPT intercept ($b = .34$, $p < .001$) and not the linear or quadratic time trajectory, indicating that women with higher chronic stress at study entry reported significantly greater physical symptom bother across assessments (see Table 4). Effect size estimates indicate that the addition of chronic stress to a model with covariates resulted in a 9% reduction in

Table 4 Longitudinal growth models of physical symptom bother (BCPT) association with chronic and episodic stress

Variable	Study entry chronic stress Est. (*SE*)	Post-diagnosis episodic stress Est. (*SE*)	Chronic stress and post-diagnosis episodic stress Est. (*SE*)	Chronic stress and pre-diagnosis episodic stress Est. (*SE*)
Intercept				
Intercept	.74*** (.13)	.84*** (.14)	.74*** (.13)	.74*** (.13)
Age	−.01** (.00)	−.01*** (.00)	−.01** (.00)	−.01** (.00)
Married (ref = no)	.09* (.04)	.07 (.04)	.09* (.04)	.09* (.04)
Ethnicity (ref = non-Latina white)	.05 (.06)	.05 (.06)	.05 (.06)	.05 (.06)
Income	.06*** (.02)	.04* (.02)	.06*** (.02)	.06** (.02)
Employment (ref = employed)				
Retired	−.05 (.05)	−.09 (.05)	−.05 (.05)	−.05 (.05)
Unemployed	.16*** (.05)	.17** (.05)	.16** (.05)	.16*** (.05)
Physical comorbidities	.04*** (.01)	.05*** (.01)	.04*** (.01)	.04*** (.01)
Site (ref = Arizona)	.17*** (.04)	.16*** (.04)	.15** (.04)	.34*** (.05)
Stage	.01 (.02)	.00 (.02)	.01 (.02)	.01 (.02)
Chemotherapy[a] (ref = no)	−.01 (.03)	−.01 (.03)	−.01 (.03)	−.01 (.03)
Radiation[a] (ref = no)	−.08* (.03)	−.09* (.03)	−.08* (.03)	−.08* (.03)
Herceptin[a] (ref = no)	.07 (.04)	.06 (.04)	.07 (.04)	.07 (.04)
Endocrine therapy[a] (ref = no)	−.00 (.03)	−.00 (.03)	−.00 (.03)	−.00 (.03)
Last treatment	.02* (.01)	.03* (.01)	.02* (.01)	.02* (.01)
Study entry chronic stress	.34*** (.05)	–	.33*** (.05)	.34*** (.05)
Post-diagnosis episodic stress	–	.04** (.01)	.03* (.01)	–
Pre-diagnosis episodic stress	–	–	–	.01 (.01)
Linear trajectory				
Intercept	.07 (.17)	.07 (.17)	.07 (.17)	.07 (.17)
Age	.00* (.00)	.00* (.00)	.00* (.00)	.00* (.00)
Married (ref = no)	−.07 (.04)	−.07 (.04)	−.07 (.04)	−.07 (.04)
Ethnicity (ref = non-Latina white)	−.29 (.17)	−.30 (.17)	−.23 (.17)	−.29 (.17)
Income	−.05** (.02)	−.05** (.02)	−.05** (.02)	−.05** (.02)
Site	−.19 (.12)	−.19 (.12)	−.19 (.12)	−.19 (.12)
Last treatment	−.01 (.01)	−.01 (.01)	−.01 (.01)	−.01 (.01)
Chemotherapy[a] (ref = no)	.43** (.17)	.43** (.17)	.42* (.16)	.43** (.17)
Radiation[a] (ref = no)	.14 (.08)	.15 (.08)	.14 (.08)	.14 (.08)
Herceptin[a] (ref = no)	−.08 (.06)	−.07 (.06)	−.08 (.06)	−.08 (.06)
Endocrine therapy[a] (ref = no)	−.08 (.12)	−.10 (.12)	−.09 (.12)	−.08 (.12)
Quadratic trajectory				
Intercept	−.41*** (.11)	−.41*** (.11)	−.41*** (.11)	−.41*** (.11)
Ethnicity (ref = non-Latina white)	.38** (.15)	.38** (.15)	.38* (.15)	.34** (.15)
Site	.33** (.11)	.33** (.11)	.33** (.11)	.33** (.11)
Chemotherapy[a] (ref = no)	−.54* (.23)	−.55* (.24)	−.53* (.23)	−.54* (.23)
Endocrine therapy[a] (ref = no)	.15 (.10)	.16 (.10)	.15 (.10)	.15 (.10)

Pre-diagnosis episodic stress was reported by participants at study entry and was not a significant predictor of BCPT; interactions between chronic stress and episodic stress pre- and post-diagnosis also were not significant predictors of BCPT (longitudinal growth models not shown)

Est. = regression coefficient; *SE* standard error; *BCPT* Breast Cancer Prevention Trial Symptom Scale

* $p < .05$. ** $p < .01$. *** $p < .001$

[a] Indicates variable is time-varying, all other variables are time-invarying

residual variance of the Level 2 intercept ($R^2 = .09$). Post-diagnosis episodic stress predicted the BCPT intercept ($b = .04$, $p < .01$) and not the linear or quadratic time trajectory, such that women with higher episodic stress shortly after diagnosis reported significantly greater symptom bother across time. The addition of post-diagnosis episodic stress to a model with covariates resulted in a 2% reduction in residual variance of the Level 2 intercept ($R^2 = .02$). Episodic stress prior to breast cancer diagnosis did not significantly predict the intercept or the linear or quadratic time trajectory.

With chronic stress and post-diagnosis episodic stress in the same model, significant main effects of both chronic stress ($b = .33$, $p < .001$) and post-diagnosis episodic stress ($b = .03$, $p < .05$) emerged on symptom bother (see Table 4). Higher levels of both types of stress were significantly related to greater symptom bother over time. Neither of these stress measures predicted the linear or quadratic time trajectory. The addition of chronic stress and post-diagnosis episodic stress to a model with only covariates resulted in a 10% reduction in residual variance of the Level 2 intercept ($R^2 = .10$). With chronic stress and pre-diagnosis episodic stress in the same model, there was a significant main effect of chronic stress on symptom bother ($b = .34$, $p < .001$); pre-diagnosis episodic stress was not significantly related to symptom bother, and neither stress measure predicted the linear or quadratic time trajectory. Interactions between chronic stress and pre-diagnosis episodic stress and between chronic stress and post-diagnosis episodic stress did not predict the intercept or the linear or quadratic time trajectory.

Discussion

As hypothesized, both chronic stress and episodic stress during the first months after breast cancer diagnosis predicted greater physical symptom bother throughout the following year. Episodic stress reported to have occurred in the 6 months prior to diagnosis was unrelated to symptom bother. Contrary to expectation, no significant interactions emerged between chronic and episodic stress on symptom bother. Instead, when examined in the same model, both chronic and post-diagnosis episodic stress emerged as unique predictors of subsequent bothersome physical symptoms. These results suggest that stressful life events occurring in the context of ongoing chronic stress have a unique rather than a multiplicative association with future bothersome physical symptoms.

Our findings are consistent with the biobehavioral model of cancer stress and disease (Andersen et al., 1994) and empirical evidence suggesting that life stress negatively influences adjustment to cancer (Burgess et al., 2005; Golden-Kreutz et al., 2005; Golden-Kreutz & Andersen, 2004; Grassi et al., 1997; Kornblith et al., 2001). To our knowledge, only one previous study (Golden-Kreutz et al., 2005) examined life stress as a predictor of physical health-related adjustment to breast cancer. In that study, stressful life events prior to diagnosis and perceived overall and cancer-related stress after initial surgery for breast cancer predicted poorer physical health-related quality of life during and after adjuvant treatment.

Findings from the current study add to the knowledge base by elucidating the relative influences of chronic and episodic stress on bothersome physical symptoms in breast cancer. When examined in the same model, chronic and post-diagnosis episodic stress each remained significant predictors of physical symptom bother. Calculations of unique effect sizes of each type of stress suggest that chronic stress is a stronger predictor of physical symptom bother than post-diagnosis episodic stress. Chronic stress accounted for an additional 8% of variance when added to a model with post-diagnosis episodic stress and covariates, whereas post-diagnosis episodic stress added 1% of variance to a model with chronic stress and covariates.

Whereas episodic stress occurring shortly after diagnosis (between diagnosis and study entry, a period of approximately 2 months) predicted bothersome physical symptoms over time, stressful life events reported to have occurred during the 6 months prior to diagnosis were unrelated to symptom bother. These results are consistent with research on the time-limited effects of episodic stressors (Suh et al., 1996). Prior to diagnosis, women may be better equipped to cope with, and perhaps resolve, stressful life events. The period shortly after diagnosis, however, presents many challenges that may preclude effective management and resolution of stressors. After breast cancer diagnosis, women often must make difficult treatment-related decisions and plan for changes in employment and other life roles (Holland et al., 2015). During this time, coping with additional stressors such as a family member's illness or a financial hardship may be particularly trying. Indeed, results of the current study suggest that stressful life events occurring shortly after diagnosis have a lasting impact on physical symptom bother throughout the following year. Another possible explanation for the lasting impact of episodic stress occurring shortly after diagnosis is that women who experience stressful life events at study entry are more likely to experience additional events during the follow-up period. Severity ratings for episodic stress during the approximately 8 months prior to study entry and the subsequent 9 months, however, were only weakly correlated.

How does life stress affect cancer-related physical symptoms such as pain and fatigue? Although the current study did not examine mediators of this relationship, the biobehavioral

model of cancer stress and disease (Andersen et al., 1994) describes plausible mechanisms. Stressful life events and longer-term chronic stressors are associated with decrements in immune functioning (Herbert & Cohen, 1993), which may influence treatment response and treatment-related side effects. Stress may also negatively affect health behaviors such as diet, physical activity, and alcohol use; for cancer patients, unhealthy behaviors may have important consequences for physical health-related adjustment (Andersen et al., 1994). The model of conservation of resources (Hobfoll, 1989) offers another useful lens through which to consider the effects of stress on treatment-related side effects. Women experiencing chronic stress and recent episodic stressors may have depleted psychological (e.g., mastery, self-esteem), social, and material resources to cope effectively with the cancer diagnosis, and therefore may experience more distress related to side effects of treatment. Indeed, one study found that, among women with breast cancer who had recently completed primary oncologic treatment, cancer-related emotional approach coping (i.e., coping through emotional processing and expression) was adaptive only under conditions of low stress (Low et al., 2006). Depression may also mediate the effects of life stress on bothersome physical symptoms (Hammen, 2005). Future research is needed to test these and other possible mechanisms.

Strengths and limitations

This study has a number of strengths. In a relatively large sample of women newly diagnosed with breast cancer, physical symptom bother was assessed longitudinally, which allowed for characterization of relations among life stress and bothersome symptoms over time. Whereas previous studies have employed self-report measures of perceived overall stress (Golden-Kreutz et al., 2005; Golden-Kreutz & Andersen, 2004) and/or life events checklists to assess the occurrence or impact of stressful life events (Golden-Kreutz et al., 2005; Golden-Kreutz & Andersen, 2004; Grassi et al., 1997; Kornblith et al., 2001; Low et al., 2006), the present study used a detailed interview to obtain a comprehensive assessment of the severity of chronic stress in various life domains and the impact of stressful life events based on the context in which the events occurred.

Discussion of study limitations is warranted. On average, women in the current study were younger ($M = 56.4$ years) than the population median age of breast cancer diagnosis of 61 years (American Cancer Society, 2015). Although the ethnic makeup in the study reflected local recruitment populations, African American women were under-represented and Latinas were over-represented relative to the breast cancer population in the U.S. Therefore, the findings cannot by generalized to diverse groups without further examination.

Conclusions and future directions

Our findings suggest that ongoing chronic stress and episodic stress occurring shortly after breast cancer diagnosis are important and unique predictors of persistent and bothersome physical symptoms during and after breast cancer treatment. Screening in the months after diagnosis for ongoing chronic stress and recent stressful life events may help identify women at risk for experiencing distress related to physical symptoms during and after treatment. Patients experiencing stress during cancer may have fewer resources to cope with ongoing physical symptoms and, as such, are especially likely to benefit from careful attention to symptom management by their clinicians. Furthermore, findings suggest that interventions to prevent or ameliorate bothersome cancer-related physical symptoms should begin soon after breast cancer diagnosis and might be more effective if they address ongoing non-cancer-related stress in women's lives. This work advances knowledge regarding the role of life stress in adjustment to cancer and informs applied research that aims to identify at-risk women recently diagnosed with breast cancer for timely intervention.

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Compliance with ethical standards

Conflict of interest Lauren N. Harris, Margaret R. Bauer, Joshua F. Wiley, Constance Hammen, Jennifer L. Krull, Catherine M. Crespi, Karen L. Weihs, and Annette L. Stanton declare that they do not have any conflict of interest.

Human and animal rights and Informed consent All procedures performed in this study were in accordance with the ethical standards of the relevant Institutional Review Boards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients for being included in the study.

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