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Sympathetic and parasympathetic activity in cancer-related fatigue: More evidence for a physiological substrate in cancer survivors

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Summary Fatigue is a notable clinical problem in cancer survivors, and understanding its pathophysiology is important. This study evaluated relationships between fatigue and both sympathetic and parasympathetic nervous system activity in breast cancer survivors. Norepinephrine and heart rate variability (HRV) were evaluated at rest, as well as during and after a standardized laboratory speech and mental arithmetic stressor. The participants, 109 women who had completed treatment for stage 0—IIIA breast cancer within the past two years, were at least two months post surgery, radiation or chemotherapy, whichever occurred last. Women who reported more fatigue had significantly higher norepinephrine and lower HRV before and after the stressor than their less fatigued counterparts. Fatigue was not related to treatment or disease variables including treatment type, cancer stage, time since diagnosis, and time since treatment.

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Importantly, the relationship between HRV and cancer-related fatigue was sizeable. Based on research that has demonstrated characteristic age-related HRV decrements, our findings suggest a 20-year difference between fatigued and non-fatigued cancer survivors, raising the possibility that fatigue may signify accelerated aging. Furthermore, lower HRV and elevated norepinephrine have been associated with a number of adverse health outcomes; accordingly, fatigue may also signal the need for increased vigilance to other health threats.

Fatigue is the most common problem among long-term cancer survivors (Bower et al., 2006a), as well as the symptom that interferes most with their daily life (Cleeland et al., 2003; Ganz et al., 2002). Fatigue adversely affects overall quality of life, as well as many daily activities including mood, the sleep-wake cycle, and personal relationships (Bower et al., 2002; Collado-Hidalgo et al., 2006; Lawrence et al., 2004). Fatigue is a normal and expected response to chemotherapy and radiation (Smets et al., 1993). However, fatigue may persist many years beyond cancer treatment in a substantial number of cancer survivors (Prue et al., 2006). For example, in a longitudinal study of 763 breast cancer survivors, 34% were fatigued 5—10 years after diagnosis, compared to 35% 1—5 years after diagnosis; 21% of the women were fatigued at both assessments, suggesting more severe or persistent fatigue among a significant proportion of cancer survivors (Bower et al., 2006b).

In general, neither disease type nor treatment variables have demonstrated reliable associations with fatigue in cancer survivors. Specifically, type of cancer, disease stage at diagnosis, tumor size, number of nodes involved, presence and site of metastases, time since diagnosis, the type or extent of cancer treatment (including chemotherapy regime, dose, and cycles, and type of radiation), length of treatment, and time since treatment completion do not consistently predict the occurrence or severity of fatigue among survivors (Prue et al., 2006).

Autonomic nervous system functioning may play an important role in cancer-related fatigue. Higher parasympathetic activity facilitates energy conservation, while prolonged heightened sympathetic activity puts undue energy demands on the body (Thayer and Sternberg, 2006). The combination of sympathetic overactivity and parasympathetic underactivity has been linked with a number of adverse health outcomes (Mark, 1996; Thayer and Lane, 2007). In non-cancer populations, sympathetic overactivity and parasympathetic underactivity have been linked to fatigue (Segerstrom and Nes, 2007; Tak et al., 2009). Both higher sympathetic activity and lower parasympathetic activity also facilitate activation of the proinflammatory cytokine network; fatigued breast cancer survivors have higher levels of circulating proinflammatory cytokines compared to their nonfatigued counterparts (Bower et al., 2007). Accordingly, sympathetic overactivity and parasympathetic underactivity may be important biomarkers of cancer-related fatigue and may also have an etiological role.

The variability in heart rate that is attributable to respiration is directly mediated by the vagus nerve and serves as a marker for parasympathetic activity (often referred to as vagal tone) (Berntson et al., 1993). Healthy adults with lower HRV had more fatigue when performing cognitively demanding tasks than those with higher HRV (Segerstrom and Nes, 2007). In addition, lower HRV was associated with driver-related fatigue (Egelund, 1982), as well as greater fatigue after prolonged exercise (Hautala et al., 2001). Low vagal tone is also associated with an exaggerated proinflammatory profile due to the cholinergic anti-inflammatory pathways of the parasympathetic nervous system (Tracey, 2009).

Norepinephrine is the principal sympathetic nervous system neurotransmitter. Adolescents reporting chronic fatigue had higher levels of norepinephrine than controls (Wyller et al., 2008). Similarly, male shift workers who had higher levels of norepinephrine reported more fatigue than those who reported less fatigue (Park et al., 2006). Norepinephrine induces transcription factor nuclear factor κB (NF-κB), an intracellular signaling molecule that regulates proinflammatory cytokine gene expression (Straub and Härle, 2005).

In healthy individuals, increased sympathetic activity and decreased parasympathetic activity represent adaptive fight-or-flight responses to stressors, followed by heightened parasympathetic and lowered sympathetic activity post-stressor (Porges, 1995). It is possible that fatigued individuals do not show these same fluctuations, making it difficult for them to meet and recover from stress-related metabolic demands.

Accordingly, the current study examined relationships between fatigue and autonomic activity at rest, as well as in response to a standardized laboratory stressor in breast cancer survivors. Our central hypothesis was that more fatigued women would have higher norepinephrine and lower HRV than less fatigued women. We also addressed the question of whether changes in HRV and norepinephrine over time differed depending on women's level of fatigue.

1. Method

1.1. Participants

The study data were drawn from the baseline sample of a clinical trial addressing the potential benefits of yoga for breast cancer survivors, and participants were recruited through breast cancer clinics and media announcements. Women could not participate in our study if they were currently practicing yoga, took yoga classes within the last 6 months, or practiced yoga for more than 3 months over their lifetime. Eligible women had completed treatment for stage 0—IIIA breast cancer within the past two years (except for tamoxifen/aromatase inhibitors) and were at least two months post surgery, radiation, or chemotherapy (whichever occurred last). Screening exclusions included a prior history of breast or any other cancer except basal or squamous cell, more than 5 h a week of vigorous physical exercise, a body mass index (BMI) of 40 or greater, diabetes, chronic obstructive

pulmonary disease, uncontrolled hypertension, evidence of liver or kidney failure, and symptomatic ischemic heart disease. The Ohio State Biomedical Research Review Committee approved the project; all subjects gave written informed consent prior to participation. Out of the 109 participants enrolled, 105 had norepinephrine data and 84 had HRV data.

1.2. Procedure

When women arrived at the Clinical Research Center (a hospital research unit) at 900 h, a catheter was inserted in their arm. Once they had eaten a standardized breakfast (after fasting since midnight) and completed questionnaires (approximately 25 min after catheter insertion), they sat quietly in a chair for 20 min. A 10 min period in the middle of this baseline relaxation period provided baseline tonic HRV data. At the end this relaxation period, blood was drawn to assess resting norepinephrine levels.

Next, women participated in the Trier Social Stress Test (Kirschbaum et al., 1993), a well-validated laboratory stressor that provokes reliable changes in autonomic functioning (Kudielka et al., 2004). After spending 10 min preparing a speech about why they were the best candidate for a job, a research assistant escorted them to a room where they saw a microphone, video camera, and an ''audience'' panel of 2 individuals wearing white laboratory coats. While seated, the women gave their 5-min speech and then performed mental arithmetic serial subtraction tasks for 5 min in front of this panel. The time spent in front of the Trier panel provided the stress HRV data. A blood sample drawn immediately after the Trier provided data on norepinephrine stress responses.

After the Trier panel left the room (approximately 1 min), the next 10 min served as the HRV recovery period (Altemus et al., 2001). Then, 35 min later (45 min post baseline), another blood sample assessed norepinephrine recovery.

1.3. Heart rate variability

HRV was continuously measured non-invasively with the Polar s810 wristwatch and Wearlink 31 belt band; the 1000 Hz sampling rate provides valid and reliable ECG data (Gamelin et al., 2006; Nunan et al., 2009). Before analyzing HRV, we preprocessed the raw interbeat intervals for artifacts using KUBIOS HRV analysis software (Tarvainen et al., 2009). For every phase of the experiment, the KUBIOS software produced values for vagally mediated (parasympathetic) HRV using the time-domain method, square root of mean successive differences (RMSSD) between R-Waves, and the frequency-domain method, high frequency power (HF; 0.15—0.40 Hz). Higher scores on both measures indicate higher vagally mediated HRV. RMSSD is determined by calculating the differences between consecutive interbeat (RR) intervals before squaring and summing them; the values are then averaged and the square root obtained. HF HRV is determined by performing spectral analysis to estimate the power spectrum density for the RR interval series, and then extracting the frequency band of interest (Malik et al., 1996; Stein et al., 1994). All procedures followed the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology (Malik et al., 1996).

1.4. Norepinephrine

Plasma samples were frozen at −70° C and assayed by HPLC with ElectroChemical Detection using Standards and Chemistry (alumina extraction) from Thermo-Alko. The intra-assay variation for norepinephrine is 3%, the inter-assay variation is 6%, and sensitivity is 15 pg/ml.

1.5. Measures

Cancer-related fatigue manifests in a wide range of behavioral, cognitive, somatic, and affective symptoms (Portenoy and Itri, 1999). Thus, we adopted a multidimensional fatigue scale to assess a full range of fatigue symptoms. The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) is a 30-item scale that assesses five dimensions of fatigue (Stein et al., 2004, 1998). The total score represents the sum of four subscales (general fatigue, physical fatigue, emotional fatigue, and mental fatigue) minus the vigor scale. Alphas for individual subscales ranged from 0.86 to 0.92. Alpha for the total score was .90.

The RAND SF-36 vigor/vitality scale (Ware et al., 1992) was used as a secondary fatigue measure because of its use in a series of studies assessing the biological mechanisms underlying cancer-related fatigue (Bower, 2007; Bower et al., 2005a, 2006a). Standardized scores on the RAND SF-36 vigor/vitality scale range from 0 to 100, with higher scores indicating less fatigue (Ware et al., 1992). Fatigued breast cancer survivors who score below 50 have had higher inflammation than those who score above 50, and thus we used this same cut to create a ''case'' categorical variable (Bower et al., 2005a,b).

The Charlson index (Charlson et al., 1994), the most widely used comorbidity index for predicting mortality, was used to assess comorbidities. The measure assigns weights to 19 comorbid conditions based on their potential influence on one-year mortality in breast cancer patients.

The Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire assessed the weekly frequency and duration of various physical activities. Excellent for middle-aged and older populations, it has a solid validational history, including use with cancer populations (Demark-Wahnefried et al., 2003a). We used the moderate-plus index (minutes of moderate to very hard intensity activities).

The Center for Epidemiological Studies Depression Scale (CES-D) has been used extensively as a brief measure of depressive symptomatology (Basco et al., 1997; Radloff, 1977). Studies have shown acceptable test-retest reliability and excellent construct validity (Basco et al., 1997). As the CES-D has also distinguished depressed from non-depressed participants in community and clinical samples, discriminative validity appears acceptable as well (Basco et al., 1997). It has been widely used in cancer studies (Demark-Wahnefried et al., 2003b).

1.6. Analytic method

All analyses were run using a mixed models regression program employing restricted maximum likelihood estimation. Both HRV and norepinephrine were log-transformed prior to

Table 1 Demographic and medical characteristics of fatigued and nonfatigued breast cancer survivors (categorized based on SF-36 score).

Characteristic	Overall (n = 109)		Fatigued (n = 57)		Nonfatigued (n = 52)	
	No	%	No	%	No	%
RMSSD, untransformed						
Baseline						
Mean (SD)	25.510 (15.504)		22.145 (13.327)		28.875 (16.905)	
Stress						
Mean (SD)	17.509 (10.825)		16.023 (10.802)		18.891 (10.787)	
Recovery						
Mean (SD)	21.536 (14.287)		18.324 (11.513)		24.237 (15.889)	
RMSSD, natural log						
Baseline						
Mean (SD)	3.072 (0.589)		2.936 (0.577)		3.208 (0.576)	
Stress						
Mean (SD)	2.666 (0.661)		2.564 (0.671)		2.762 (0.645)	
Recovery						
Mean (SD)	2.882 (0.619)		2.735 (0.601)		3.007 (0.613)	
Norepinephrine, untransformed						
Baseline						
Mean (SD)	507.24 (288.81)		511.19 (281.26)		502.54 (300.45)	
Stress						
Mean (SD)	673.32 (300.10)		697.87 (301.58)		645.64 (299.23)	
Recovery						
Mean (SD)	609.08 (311.14)		612.25 (315.41)		605.50 (309.68)	
Norepinephrine, natural log						
Baseline						
Mean (SD)	6.107 (0.481)		6.123 (0.469)		6.088 (0.498)	
Stress						
Mean (SD)	6.423 (0.422)		6.467 (0.401)		6.374 (0.443)	
Recovery						
Mean (SD)	6.303 (0.459)		6.316 (0.436)		6.289 (0.488)	
Age, years						
Mean (SD)	51.661 (9.378)		51.333 (8.234)		52.019 (10.562)	
Depressive symptoms (CES-D)						
Mean (SD)	10.431 (8.191)		14.544 (8.492)		5.923 (4.826)	
Smoking status	7	6.4	4	7.0	3	5.8
BMI						
Mean (SD)	27.507 (5.588)		28.358 (5.580)		26.574 (5.499)	
Cardiac medication	13	11.9	12	21.1	1	1.9
Activity, hours per week						
Mean (SD)	7.117 (6.379)		6.539 (6.100)		7.750 (6.673)	
MFSI-SF fatigue						
Mean (SD)	13.376 (21.030)		26.053 (19.601)		−0.519 (11.758)	

Energy/fatigue scale, RAND36						
Mean (SD)	50.459 (20.711)		34.211 (13.255)		68.269 (9.846)	
Ethnicity						
Asian	2	1.8	1	1.6	1	1.9
Black	9	8.0	5	8.2	4	7.7
Latino	4	3.5	4	6.6	0	0.0
White	98	86.7	51	83.6	47	90.4
Marital status						
Single	16	14.7	6	10.5	10	19.2
Married	78	71.6	40	70.2	38	73.1
Separated/divorced	13	11.9	11	19.3	2	3.9
Widowed	2	1.8	0	0.0	2	3.9
Education level						
High school or less	8	7.3	5	8.8	3	5.8
Some college	25	22.9	20	35.1	5	9.6
College or university graduate	34	31.2	10	17.5	24	46.2
Postgraduate	42	38.5	22	38.6	20	38.5
Employment status						
Employed full or part time	73	67.0	41	71.9	32	61.5
Unemployed	19	17.4	8	14.0	11	21.2
Retired	17	15.6	8	14.0	9	17.3
Income level						
$0—$25,000	4	3.7	3	5.3	1	1.9
$25,000—$50,000	15	13.8	9	15.8	6	11.5
$50,000—$75,000	22	20.2	13	22.8	9	17.3
$75,000—$100,000	30	27.5	16	28.1	14	26.9
>$100,000	28	25.7	14	24.6	14	26.9
No report	10	9.2	2	3.5	8	15.4
Type of treatment						
Surgery only	12	11.0	7	12.3	5	9.6
Surgery + radiation	24	22.0	12	21.1	12	23.1
Surgery + chemotherapy	27	24.8	15	26.3	12	23.1
Surgery + radiation + chemotherapy	46	42.2	23	40.4	23	44.2
Cancer stage						
Stage 0	8	7.3	2	3.5	6	11.5
Stage I	48	44	28	49.1	20	38.5
Stage IIA	30	27.5	16	28.1	14	26.9
Stage IIB	13	11.9	6	10.5	7	13.5
Stage IIIA	10	9.2	5	8.8	5	9.6
HER2 receptor status						
Positive	23	21.1	11	19.3	12	23.1
Negative	73	67.0	41	71.9	32	61.5
Unknown	13	11.9	5	8.8	8	15.4

Table 1 (*Continued*)

Characteristic	Overall ($n = 109$)		Fatigued ($n = 57$)		Nonfatigued ($n = 52$)	
	No	%	No	%	No	%
Progesterone receptor status						
Positive	70	64.2	36	63.2	34	65.4
Negative	32	29.4	17	29.8	15	28.9
Unknown	7	6.4	4	7.0	3	5.8
Estrogen receptor status						
Positive	82	75.2	42	73.7	40	76.9
Negative	20	18.4	11	19.3	9	17.3
Unknown	7	6.4	4	7.0	3	5.8
Tamoxifen/aromatase inhibitors	36	33.0	18	31.6	18	34.6
Months since diagnosis						
Mean (SD)	17.587 (7.975)		18.614 (8.962)		16.462 (6.635)	
Months since last treatment						
Mean (SD)	10.890 (7.814)		11.842 (8.539)		9.846 (6.864)	

any analyses. For each HRV analysis, we conducted separate analyses using HRV time domain and frequency domain measures as dependent variables. However, because the results did not differ across the two indices and the time domain and frequency domain measures were so highly correlated, $r = 0.94$ $p < 0.001$, we present only the time domain data. For each analysis, we adjusted for key potential confounds including age, BMI, and physical activity as continuous variables and modeled their relationship to HRV and norepinephrine as linear; we also included two indicator variables to represent smoking status (1 = current smoker and 0 = nonsmoker) and cardiovascular medication status (use of beta blockers, diuretics, or calcium channel blockers vs. none). We examined residuals from all analyses to confirm that they were distributed normally.

We hypothesized that women who were more fatigued would have lower levels of resting HRV and higher levels of norepinephrine compared to those who were less fatigued. Preliminary analyses revealed that HRV and norepinephrine were not associated with each other $r = -0.02$ $p = 0.85$.

For the MFSI-SF continuous fatigue data, we ran mixed-model linear regressions. For SF-36 analyses, women were classified as fatigued or not (1 = fatigued and 0 = not fatigued), and thus we used mixed-model ANCOVAs.

We analyzed the data from the baseline, stress, and recovery segments of norepinephrine and HRV because we also investigated whether or not women who reported more fatigue have a different autonomic profile in response to the stressor than women who reported less fatigue. When we ran separate preliminary repeated measures analyses for both norepinephrine and HRV, the correlations over the three segments varied considerably. Hence, we employed an unstructured within-subjects covariance matrix for all repeated measures analyses.

2. Results

Table 1 reports descriptive information for the 109 participants.

Fatigued and nonfatigued participants did not differ by treatment type, cancer stage, time since diagnosis, time since last treatment, age, activity level, Her2 receptor status, progesterone receptor status, estrogen receptor status, tamoxifan/aromatase use, or albumin and hemoglobin levels. The 6 participants who had any Charlson-rated comorbidities were divided equally between the fatigued and nonfatigued groups. As would be expected fatigued women were more likely to be unmarried ($\chi^2 = 9.1$, $p = 0.03$), have a lower socioeconomic status as indexed by education ($\chi^2 = 1.4$, $p = 0.002$), have a marginally higher BMI ($t = -1.7$, $p = 0.10$), and report more depressive symptoms ($t = -6.6$, $p < 0.001$), all previously identified correlates of fatigue (Bower, 2008). Of note, there was considerable overlap between the MFSI-SF fatigue measure and depressive symptoms ($r = .80$ $p < 0.001$) fatigue and depression are overlapping constructs at both a conceptual and measurement level (Morrow et al., 2005; Stein et al., 1998).

Table 2 summarizes the results for the first hypothesis.

As predicted, HRV was lower among more fatigued women compared to those who were less fatigued based on scores from the MFSI-SF. Mean HRV was also significantly lower in fatigued women compared to the nonfatigued women based

Table 2 Heart rate variability and norepinephrine differences at baseline based on MFSI-SF and SF-36 fatigue measures.

	LnHRV	LnNorepinephrine
MFSI-SF		
F-test	8.25	10.18
DF	1,77	1,98
Beta	−0.009	0.007
p-value	0.005	0.002
SF-36		
F-test	6.41	0.67
DF	1,77	1,98
Fatigued (mean)	2.900	6.145
Not fatigued (mean)	3.244	6.067
Contrast	−0.345	0.078
p-value	0.013	0.416

on the SF-36. Norepinephrine levels were higher among more fatigued women compared to those who were less fatigued based on scores from the MFSI-SF. Norepinephrine levels did not differ between fatigued and non-fatigued women based on the SF-36. In addition, we performed post hoc analyses to examine whether any particular subscale of the multidimensional MFSI-SF was driving the associations. Zero-order correlations between HRV and each fatigue subscale, as well as between norepinephrine and each fatigue subscale, revealed that no single subscale was driving the association.

Table 3 summarizes the results of the repeated measures analysis that assessed whether changes in HRV and norepinephrine over time differed depending on women's level of fatigue using the MFSI-SF.

Table 4 summarizes the results of the repeated measures analysis that assessed whether changes in HRV and norepinephrine over time differed depending on women's level of fatigue using the SF-36.

There was no evidence of a fatigue by period interaction in the repeated measures analyses that assessed whether changes in HRV over time differed depending on women's level of fatigue. HRV decreased from the baseline period to the stress period, but the decreases were unrelated to fatigue. HRV increased from the stress period to the recovery period, but the increases were unrelated to fatigue. Even so, there was evidence of systematic differences between fatigued and non-fatigued women. Breast cancer survivors who reported more fatigue on the MFSI-SF had significantly lower HRV during both the baseline and recovery periods than those who were less fatigued. The SF-36 fatigue scale yielded the same pattern of results. Thus, although we did not find fatigue-related HRV differences in response to the stressor, we did find consistent evidence that fatigue was associated with lower HRV both before and after the stressor as measured by both the MFSI-SF and the SF-36 (Fig. 1).

There was no evidence of a fatigue by period interaction in the repeated measures analyses that assessed whether changes in norepinephrine over time differed depending on women's level of fatigue. For both the MSFI-SF and the SF-36, norepinephrine increased from the baseline period to the stress period, but the increases were unrelated to fatigue. Norepinephrine decreased from the stress period to the recovery period, but the decreases were unrelated to fatigue. There was evidence of systematic differences between fatigued and non-fatigued women based on the MFSI-SF but not the SF-36. Specifically, breast cancer survivors who reported more fatigue on the MFSI-SF had significantly higher norepinephrine during baseline, stressor, and recovery. Hence, although we did not find fatigue-related norepinephrine differences in responses to the stressor, we did find consistent evidence that fatigue was associated with higher norepinephrine as measured by the MFSI-SF (Fig. 2).

For each model, we ran additional ancillary analyses controlling for treatment type, cancer stage, and time since treatment. All significance levels remained the same.

3. Discussion

Cancer-related fatigue is a notable clinical problem that can affect cancer survivors many years beyond treatment, and thus a better understanding of the factors that contribute to its development and maintenance is important. Women who reported more fatigue had significantly higher norepinephrine and lower HRV before and after the stressor than women who reported less fatigue, providing evidence that fatigue is associated with a maladaptive autonomic profile

Table 3 Heart rate variability and norepinephrine differences across time based on MFSI-SF fatigue measure.

Effect	Time point	LnHRV		LnNorepinephrine	
		Estimate	*p*	Estimate	*p*
MFSI-SF fatigue		−0.008	0.010	0.006	0.004
Period	Baseline				
	Stressor	−0.441	<0.001	0.325	<0.001
	Recovery	−0.175	0.004	0.204	<0.001
MFSI-SF × period	Baseline				
	Stressor	0.002	0.536	−0.002	0.164
	Recovery	−0.002	0.377	−0.001	0.467
Change per unit fatigue	Baseline	−0.008	0.010	0.004	0.025
	Stressor	−0.006	0.079	0.005	0.010
	Recovery	−0.010	0.002	0.006	0.004
Slope change per unit fatigue across time points	Baseline to stressor	0.002	0.536	0.001	0.481
	Stressor to recovery	−0.004	0.095	0.001	0.467

Table 4 Heart rate variability and norepinephrine differences across time based on the SF-36 fatigue measure.

Dependent variable: LnHRV
Type 3 tests of fixed effects

Effect	Fatigue	Period	Interaction
F-test	5.60	21.51	0.35
DF	1,77	2,77	2,77
p-value	0.021	<0.0001	0.703

Dependent variable: LnHRV
Means for the fatigue (SF36 cut at 50) × period interaction

	Baseline	Stressor	Recovery	Stressor−Baseline	Recovery−stressor
Fatigued	2.913	2.537	2.712	−0.376	0.175
Not fatigued	3.236	2.780	3.038	−0.456	0.258
Contrast	−0.322	−0.243	−0.326	0.080	−0.083
p-value	0.020	0.106	0.022	0.533	0.412

Dependent variable: LnNorepinephrine
Type 3 tests of fixed effects

Effect	Fatigue	Period	Interaction
F-test	0.73	64.72	0.42
DF	1,98	2,98	2,98
p-value	0.394	<0.0001	0.661

Dependent variable: LnNorepinephrine
Means for the fatigue (SF36 cut at 50) × period interaction

	Baseline	Stressor	Recovery	Stressor−baseline	Recovery−stressor
Fatigued	6.138	6.458	6.326	0.320	−0.132
Not fatigued	6.077	6.357	6.275	0.280	−0.082
Contrast	0.062	0.101	0.051	0.039	−0.050
p-value	0.508	0.230	0.571	0.478	0.382

characterized by higher sympathetic and lower parasympathetic activity. Although the magnitude of HRV and norepinephrine fluctuations during the stressor did not differ between fatigued and nonfatigued women, fatigued women had significantly lower HRV at baseline as well as during recovery from the stressor, and significantly higher levels of norepinephrine across each study period.

These findings are in accord with studies in the non-cancer literature showing relationships between autonomic functioning and fatigue. A hyperactive sympathetic nervous system and hypoactive parasympathetic nervous system puts excessive demands on the body (Brook and Julius, 2000). Over time, the body cannot meet these demands, which likely leads to a fatigued state (Thayer and Sternberg, 2006).

Furthermore, both HRV and norepinephrine prime inflammatory responses; therefore, our findings are likely tapping into the same physiological substrate as previous work linking

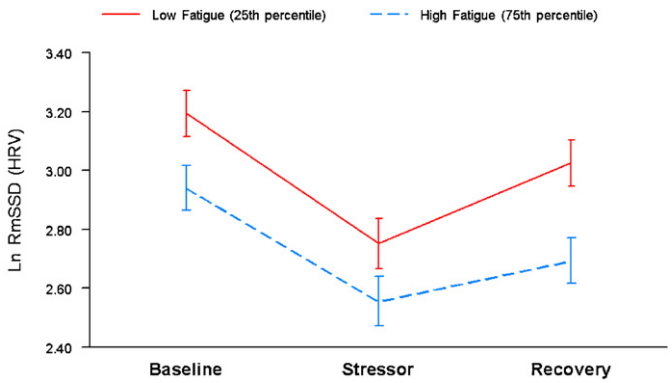

Figure 1 Mean (±SEM) HRV across experimental periods in fatigued and nonfatigued women based on the 75th and 25th percentile scores on the MFSI-SF. Although fatigued and nonfatigued survivors did not differ in the magnitude of the HRV decrement during the stressor or increment after the stressor, fatigued women had significantly lower HRV at baseline as well as during recovery from the stressor.

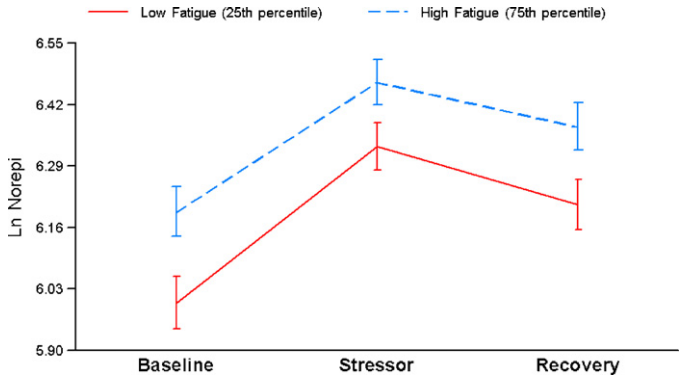

Figure 2 Mean (±SEM) norepinephrine across experimental periods in fatigued and nonfatigued women based on the 75th and 25th percentile scores on the MFSI-SF. Although fatigued and nonfatigued survivors did not differ in the magnitude of the norepinephrine increment during the stressor or decrement after the stressor, fatigued women had significantly lower norepinephrine at baseline as well as during recovery from the stressor.

proinflammatory cytokines to cancer-related fatigue and sickness behavior (Bower, 2007; Dantzer et al., 2008). Indeed, norepinephrine and HRV may be upstream biomarkers for inflammation and cancer-related fatigue. Mechanistically, norepinephrine-dependent adrenergic stimulation activates NF-κB, and NF-κB activates gene expression and production of proinflammatory cytokines is associated with cancer-related fatigue (Bierhaus et al., 2003). Furthermore, lower parasympathetic activity results in higher levels of inflammation in healthy populations, as well as among individuals with cardiovascular disease (Haensel et al., 2008) via cholinergic anti-inflammatory pathways that facilitate acetylcholine release (Tracey, 2009). When acetylcholine interacts with the macrophage's alpha-7 nicotinic receptor, it inhibits proinflammatory cytokine production (Tracey, 2009). Accordingly, lower HRV promotes higher levels of chronic systemic inflammation.

HRV and norepinephrine were not associated with each other; vagally mediated HRV is not generally associated with catecholamines (Sloan et al., 1996; Vlcek et al., 2008). This supports the view that PNS and SNS activity vary along independent axes of "autonomic space" (Berntson et al., 1994). Therefore, the sympathetic and parasympathetic nervous system may independently contribute to cancer-related fatigue.

Overproduction of norepinephrine and lower tonic HRV have been reliably associated with a variety of health risks (Mancia et al., 1999; Thayer and Sternberg, 2006). Elevated norepinephrine is linked to hypertension, myocardial infarction, and stroke (Mancia et al., 1999). Furthermore, it contributes to higher levels of blood lipids, blood clotting, and atherosclerosis (Folkow, 1982). Likewise, lower tonic HRV is a marker of all-cause mortality (Thayer and Sternberg, 2006); importantly, lower HRV is a well-established risk factor for cardiovascular disease even after controlling for other cardiovascular risk factors (Haensel et al., 2008). Cancer survivors have a higher incidence of cardiovascular disease than people who have not had cancer (Ganz, 2001), and one study suggested that survivors who experienced persistent fatigue had higher rates of heart disease than their nonfatigued counterparts (Bower et al., 2000). Fatigue may provide an important behavioral symptom that signals the need for increased vigilance related to cardiovascular and other health risks.

More broadly, the sizable relationship between HRV and cancer-related fatigue may signify accelerated aging. Indeed, based on research that demonstrated age-related HRV (RMSSD) reductions of 3.6 ms per decade, our findings suggest what would be equivalent of a 20 year difference between fatigued and non-fatigued cancer survivors (Antelmi et al., 2004). This notable difference underscores the importance of directly addressing fatigue as a symptom deserving of treatment.

Exercise is one of the best-documented treatments for cancer-related fatigue (Kangas et al., 2008; Morrow, 2007). Although relationships between HRV and exercise have not been studied in cancer populations, cardiovascular fitness is reliably associated with higher HRV in healthy adults, and exercise training clearly enhances HRV (Nolan et al., 2008). Accordingly, our HRV data provide a new perspective on pathways through which exercise alleviates cancer-related fatigue. Furthermore, because decreased HRV may precede a number of other risk factors (Malik et al., 1996; Thayer and Lane, 2007), exercise-enhanced HRV could provide a number of health benefits.

Breast cancer survivors were more fatigued in our sample compared to others (Bower et al., 2000; Stein et al., 1998, 2004). This likely occurred because we recruited women for a clinical trial designed to reduce fatigue as one of the primary aims, and we excluded woman who already exercised on a regular basis. The range of fatigued and non-fatigued survivors is a notable strength of the study.

Due to the cross-sectional design, we cannot say with certainty that lower HRV or higher norepinephrine leads to greater fatigue, or vice versa, a limitation of the study. It is possible that fatigued cancer survivors have lower HRV, and possibly higher norepinephrine, due to inactivity and deconditioning. Because we do not have exercise data on our women pre-diagnosis, we have no way to know how the cancer experience affected their exercise habits. Women in our sample did not differ significantly in the amount they exercised; consequently, we do not think the fatigued women had lower HRV and higher norepinephrine due to deconditioning. Moreover, when we controlled for activity level, the associations between fatigue and HRV, as well as fatigue and norepinephrine, were not attenuated.

Fatigue is a notable clinical problem in cancer survivors, and understanding its pathophysiology is very important.

Objective physiological measures of fatigue are needed, and our data suggest that HRV and norepinephrine could be important biomarkers for cancer-related fatigue and may have an etiological role.

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Conflict of interest

The authors have no financial interests or relationships that pose potential conflicts of interest with this article.

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