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Higher Vagal Activity as Related to Survival in Patients with Advanced Breast Cancer: An Analysis of Autonomic Dysregulation

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Abstract

Objective—High levels of high-frequency heart-rate variability (HF-HRV), related to parasympathetic-nervous-system functioning, have been associated with longer survival in patients with myocardial infarction, acute trauma, and in patients undergoing palliative care. From animal studies linking higher vagal activity with better immune-system functioning and reduced metastases, we hypothesized that higher HF-HRV would predict longer survival in patients with metastatic or recurrent breast cancer (MRBC).

Methods—Eighty-seven patients with MRBC participated in a laboratory task including a 5-minute resting-baseline ECG. HF-HRV was computed as the natural logarithm of the summed power spectral density of RR intervals (0.15–0.50 Hz). In this secondary analysis, of a study testing whether diurnal cortisol slope predicted survival, we tested the association between resting baseline HF-HRV on survival using Cox Proportional Hazards models.

Results—A total of 50 patients died during a median follow-up of 7.99 years. Higher baseline HF-HRV predicted significantly longer survival, with a hazard ratio=0.75 (95% confidence interval=0.60 to 0.92; $p=.006$). Visceral metastasis status and baseline HR were related to both HF-HRV and survival. However, a combination of HF-HRV and HR further improved survival prediction, with a hazard ratio of 0.64 (95% CI=0.48 to 0.85; $p=.002$).

Conclusions—Vagal activity of patients with MRBC strongly predicted their survival, extending the known predictive window of HF-HRV in cancer beyond palliative care. Vagal activity can be altered by behavioral, pharmacological, and surgical interventions and may be a promising target for extending life expectancy in patients suffering from metastasizing cancer.

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Keywords

Heart Rate Variability; Respiratory Sinus Arrhythmia; Parasympathetic Nervous System; Immune System; Cancer Survival; Breast Cancer

Introduction

Until recently, researchers studying cancer patients' psychosocial morbidity or mortality rarely examined autonomic dysregulation(1, 2). However, accumulating evidence, mainly from animal research, suggests that autonomic pathways connecting the central nervous system (CNS) with the periphery may play a role in the clinical course of cancer. Tumors often develop in conjunction with chronic inflammation and an inflammation-modulating vagal-feedback circuit from the *nucleus tractus solitarius* to the periphery has been proposed(3). It consists of 1) an afferent path sensing proinflammatory cytokine activity and informing the brain about tumorigenesis(3–6), and 2) an efferent path subsequently increasing activity and releasing acetylcholine that spurs local anti-inflammatory action by attenuating proinflammatory cytokine activity(6–8). In summary, based on recent evidence, the vagus nerve is likely involved in inflammatory regulation of tumor processes(3–7,9–13).

The high-frequency spectral component of heart-rate variability (HF-HRV), an established index of vagal functioning, has gained prominence in clinical research because of its association with mental and physical disorders(14, 15). The neurovisceral-integration model emphasizes the role of the vagal system in regulating allostasis and posits that lowered HF-HRV is associated with poor health across a variety of diseases because it reflects excess allostatic load(15). HF-HRV has also been linked to increased mortality: for example, lower HF-HRV significantly predicted shorter survival following myocardial infarction in a number of clinical and epidemiological studies(16–18). Low HF-HRV and related HRV metrics (e.g., standard deviations of normal-to-normal R-R intervals–SDNN), predicted mortality in trauma studies including in over 2000 trauma patients, regardless of anatomic location or severity of injury(19).

Though several breast cancer studies document associations between HF-HRV and depression and anxiety(1, 20, 21) and treatment adherence(22), none link it with MRBC survival. In other cancer studies, lower HF-HRV predicted shorter survival for hepatocellular carcinoma hospice patients(23), and lower SDNN (and higher heart-rate (HR)) also predicted shorter survival in hospice patients(24). Lower SDNN and/or HF-HRV also correlated with a higher colon-cancer marker carcinoembryonic antigen(25), predicted prostate cancer death(26), and predicted shorter all-cause and cancer survival in an epidemiological study of middle-aged men(27).

This evidence suggests that a measure of vagal functioning like HF-HRV may predict long-term cancer survival. In the current study, we assessed HF-HRV at baseline in a sample of 87 patients with MRBC and tested this survival hypothesis once mortality was above 50% (over the subsequent 7–8 years). These data represent a secondary analysis from a study powered to test the hypothesis that the diurnal slope of cortisol would predict survival in this sample(28) and to examine stress responses in metastatic or recurrent breast cancer

patients(1). We hypothesized that higher initial HF-HRV would be associated with longer survival. If analysis confirmed this hypothesis, it could have clinical implications: HF-HRV may help identify patients at risk of early mortality in need of special care(24). More importantly, it may point to mechanisms of disease progression that clinicians could target with behavioral, pharmacological, or surgical interventions that may increase vagal activity(29–36).

Methods

Participants

The Stanford Institutional Review Board approved all study materials insuring they conformed to HIPAA regulations. Referrals came from Stanford and Bay-Area oncologists, responses to newspaper advertisements, and word-of-mouth. Women could earn up to \$500 if they were able to complete the protocol (see(1, 37)).

From 221 women with MRBC recruited from 2002–2004, 29 were ineligible, 83 not interested, and two died before the study began. Of the remaining 107 who provided written informed consent, we determined that four patients were not eligible because of medical reasons (e.g. second primary cancer rather than MRBC). Of the 103, ten dropped out before HF-HRV assessment and we excluded 6 physiological recordings because of artifacts or technical difficulties, leaving 87 patients for analyses.

Inclusion criteria were metastatic or recurrent breast cancer; Karnofsky rating of at least 70%; residence within the Greater San Francisco Bay Area; and proficiency in English. Exclusion criteria were other active cancers within ten years (excepting basal cell or squamous cell carcinomas of the skin, or in situ cervical cancer), positive supraclavicular lymph nodes as the only metastatic lesion, a concurrent medical condition influencing short-term survival, using a corticosteroid within the month, diabetes, taking benzodiazepines, or history of major psychiatric illness requiring hospitalization or medication (except depression or anxiety).

Procedure

Patients with MRBC participated in the Trier Social Stress Task (TSST)(38), a standardized social/cognitive stressor, during which we collected 5-min of autonomic data for these analyses from a 5-min pre-stress resting baseline in upright seated position. Most studies testing vagal activity as a predictor of mortality used resting baseline values, representing a stable autonomic trait and thus chronic allostatic load. We previously reported significant associations between HF-HRV and depression(1) and sleep efficiency(36) in this sample.

Measures

Demographic and Medical Variables—Participants self-reported demographic variables (age, ethnicity, education, income) and both patients and their physicians reported on medical variables (disease-free interval, estrogen receptor status, site of metastasis/recurrence, types of treatment).

Cardiovascular Physiological Measurements and Data Reduction—

Experimenters obtained a standard Lead-II ECG sampled at 400 Hz. Placement of ECG electrodes, data recording, and reduction followed conventions and published guidelines(14). We assessed HF-HRV as heart-rate variability within the high-frequency band associated with respiration(14). Following established guidelines(39), we used 0.15–0.50 Hz frequency. We computed 5-min resting-baseline HF-HRV and mean HR, edited, and exported using ANSLAB Software (Society for Psychophysiological Research software repository, <http://www.sprweb.org>)(1, 40, 41). To compute HF-HRV, we edited heart-period values computed from Lead-II ECG signals for outliers from ectopic beats or artifact and converted them into time-series with 4 Hz resolution using cubic-spline interpolation. We linearly de-trended these, and computed power-spectral densities for each baseline period using the Welch algorithm(42), creating ensemble averages of successive periodograms. We derived averages from spectra estimated for 60-s segments, overlapping by half. For each 60-s segment, we analyzed 256 points, which includes 240 sampled points with zero padding. The segments were Hanning-windowed and subjected to fast Fourier transform. We adjusted estimates of power to account for attenuation produced by the Hanning window and normalized distributions with natural-logarithm transformation. Although respiratory variables might influence associations between vagal activity and HF-HRV (e.g.,(43)), we did not adjust for respiration, less useful in individual-difference data: individuals differ in respiratory function due to factors unrelated to vagal activity like lung size, basal metabolic rate, and respiratory pacemaker function(43).

All-Cause Mortality and Survival Data—We collected survival data from the Social Security Death Index, medical records, and family reports. This is an all-cause survival analysis; however, for all deaths reported, the immediate, underlying, or secondary cause was cancer, breast cancer, or MRBC.

Possible Confounding Measures—We assessed the role of physical activity, depression, stress, fatigue and sleep efficiency as possible confounding factors (proxies). Participants completed the Seven-Day Physical Activity Recall which classifies activities into levels by energy requirements and a calculation of metabolic units per day (METs)(44, 45), a ratio of working/resting metabolic rate: Sleep=1, light activity=1.0–2.9, moderate activity=3.0–5.0, hard activity=5.1–6.9, and very hard activity=7.0+. We aggregated METs by week and divided by seven for METs/day(46). Due to our previous finding of an association between depression and HF-HRV(1) we utilized both a continuous measure, the Beck Depression Inventory (BDI)(47), and our dichotomous measure(1). In the dichotomous measure(1), the depressed group included those with current SCID diagnoses (n=17), and women currently taking antidepressants except those prescribed primarily for sleep (n = 28). We used the Perceived Stress Scale--short form (PSS)(48) to measure previous-month perception of stress (10, 5-point Likert-type items 0=never to 4=very often). We used the MOS-SF 36 Health Survey(49) to assess fatigue by using the reversed and standardized vitality score.

Due to a previous significant finding in these data(50), we included sleep as a possible confounder. Participants wore a wrist actigraph (Micro Mini-Motionlogger, Ambulatory

Monitoring, Ardsley, NY) for three days. An actigraph detects arm movement with an accelerometer as a useful proxy for sleep/wake cycles. We stored 60-s epochs, and analyzed using Action 4 (v1.13) and ACT Millennium (beta v3.8.8.9) software (Ambulatory Monitoring, NY). We calculated sleep efficiency as the ratio of time-asleep/time-in-bed averaged over three days, times 100%.

Data Analysis

These data analyses proceeded in the logical steps necessary to test our single hypothesis, examine possible confounders or proxies, and to explore the meaning of our results. In the primary analysis, we used the Cox Proportional Hazards Model to test the effects of resting HF-HRV (as a continuous variable) at baseline on survival (Median 7.99 years). We had no hypothesis that included additional variables in this equation. To provide an indication of the strength of the effect, we show Kaplan-Meier survival curves with a median split on HF-HRV. Our analyses were not meant to explore all variables that might predict survival; rather, to test a single hypothesis, then to see whether variables that *both* correlated with HF-HRV and significantly predicted survival (therefore possible proxies by the MacArthur definition(51, 52)), could threaten our finding.

Sample descriptive data are in Table 1 with two-tailed 5% significance levels. We explored whether other baseline variables, demographic, medical, depression, stress, fatigue, physical activity, sleep efficiency, BMI, and HR, were possible proxies for another prognostic variable. We explored the associations between HF-HRV and each possible confounder using Spearman correlations, and Cox models to evaluate confounder associations with survival. We explored the joint impacts of HF-HRV and possible proxy variables one at a time (with independent variables HF-HRV, each confounder, and the interaction of HF-HRV and the confounder).

Results

At study entry participants were on average age 54.2 (SD=9.92), 77.0% Caucasian, with 39.1% below Bachelor's degree (Table 1 for demographic, medical, and study variables). Their metastases or recurrence were to chestwall (23.0%), bone (36.8%), and viscera (40.2%). All recurrent diagnoses had cancer spread to either chestwall or bone. Most had surgery (94.3%) with many having reconstructive surgery (27.6%). Most women had chemotherapy (87.4%) and radiation (82.8%), and many used hormone therapy (40.2%). Those with HF-HRV data (n=87) did not differ significantly from those without (n=16) except on disease-free interval ($p=0.014$, $d=0.83$), those with HF-HRV having shorter intervals.

Association between Baseline Resting HF-HRV and Survival

A total of 50 patients died during a median follow-up of 7.99 years. In the primary analysis, (*a priori* hypothesis) higher baseline resting HF-HRV (mean=4.17, $SD=1.33$, $Median=4.15$, $Range=0.51-7.28$) significantly predicted longer survival, $B=-0.294$, $Wald=7.51$, hazard ratio=0.75 (95% CI=0.60 to 0.92; $p=.006$; Figure 1). At 37.09 months (median survival from

the Kaplan-Meier), 50% of the lower HF-HRV group had died, but for women with higher HF-HRV only 34.88% had died.

Effect of Baseline Demographic/Medical Potential Proxy Variables on HF-HRV

Of all the possible confounders (proxies) measured, the only variables *both* significantly correlated with HF-HRV and predictive of survival were sleep efficiency(50), visceral metastases, reconstructive surgery, and higher HR (mean=81.22, *SD*=12.01, *Median*=81.01, *Range*=53.39–107.51), to which HF-HRV could possibly be a proxy (Table 2 for correlations). No other variables, including disease stage, met the proxy criteria. Therefore, we re-ran the Cox Proportional Hazards equation with HF-HRV, on possible proxies (one at a time), and their interaction with HF-HRV to test whether the finding of increased survival for HF-HRV would remain. For disease stage, the association of HF-HRV with survival was maintained in analysis that focused only on women with metastatic disease and excluded the 17 women with recurrent disease ($B = -0.276$, $Wald = 6.243$, hazard ratio=0.756; $p = .012$). When we considered sleep efficiency, or reconstructive surgery, HF-HRV remained significant. However, when we considered visceral metastasis, we found that HF-HRV may be a proxy (i.e., only the effect of visceral metastasis is significant, with HF-HRV reduced $p = .065$). When we explored this finding (Figure 2), we found that HF-HRV had little to no effect predicting survival in women with visceral metastases; however, it had a pronounced effect in the combined chestwall-or-bone metastasis group. When we considered HR, neither it nor HF-HRV was statistically significant, probably a consequence of collinearity, which results in an inability to separate the two effects on survival.

Post-Hoc Analyses

In order to disentangle HF-HRV and HR effects on survival, we conducted a principal components analysis assessing their overlap using Varimax rotation. Both variables loaded on a single factor accounting for 72.9% of the variance (HR correlated negatively with HF-HRV). Using factor scores to create a combined HF-HRV/HR variable (equivalent to standardizing each and taking the mean), we again conducted the Cox Regression on survival. Using the factor scores improved the prediction, $B = -0.447$, $Wald = 9.67$, hazard ratio=0.64 (95% CI=0.48 to 0.85; $p = .002$; Figure 3). Re-examining whether HF-HRV (now HF-HRV/HR) was proxy to visceral metastases we now found that both HF-HRV/HR ($B = -0.338$, $Wald = 4.94$, hazard ratio=0.71, $p = .026$) and visceral metastases ($B = 0.97$, $Wald = 9.78$, hazard ratio=2.63, $p = .002$) significantly predicted survival with no significant interaction.

Discussion

Based on a broad literature linking higher vagal activity to longer survival(11, 16–19, 53–58), and emerging connections between vagal modulation of immune function and cancer(2, 4, 5, 11, 13, 59–64), we tested whether resting high-frequency heart-rate variability (HF-HRV) predicted survival in women with metastatic or recurrent breast cancer. As expected, we found that higher resting HF-HRV significantly predicted longer overall survival, establishing HF-HRV as a long-term predictor of cancer survival for the first time. Our

analyses point to the theoretical and clinical importance of low HF-HRV as a risk factor for shorter survival in women with a diagnosis of MRBC.

Higher HF-HRV predicts longer survival across many medical conditions(11, 16–19,53–58, 65, 66). It may be a marker of the “inflammatory reflex,”(7)--the vagus nerve informing the brain about tumors and modulating them through feedback to neuroendocrine and immune systems(2, 4, 5, 11, 13, 59–64). Vagal activity also contributes to self-regulation of emotion and social activity(67–71), and is linked to treatment adherence in breast cancer(22). Thus, our finding may be mediated by behavioral factors such as emotional expression, social engagement and support, depression, and adherence to treatment which contribute both to higher vagal activity and to longer cancer survival(72–77).

Our findings extend previous cancer research suggesting HF-HRV-survival associations. We increase prediction time, and improve measurement using established spectral analysis. For instance, in a small-scale study of hospice patients, higher HF-HRV predicted greater 3-month survival(23), indicating (like many trauma studies) that it strongly predicts short-term survival. In prostate cancer, a small 10-s) measurement window predicted a one-year survival outcome(26). Likewise, in a study of men, higher HF-HRV predicted all-cause and cancer mortality, however measurement was substandard (a 15–30 sec manually scored ECG)(27).

We explored variables in our analyses with a potential for being involved in the relationship of HF-HRV and survival as proxies. Degree of visceral metastases appears to modulate the strength of HF-HRV in predicting survival, and should be considered in future studies. The inflammatory reflex can detect and dampen inflammation known to increase tumor growth(62, 78). But once there is significant growth in visceral organs known to facilitate this vagus nerve circuit(62), the inflammatory reflex may have limited impact.

We also found that lower HR predicted longer survival (< median 81 bpm). HR may reflect general arousal due to emotional factors such as stress(79), anxiety(80), or anger(81), and is reduced in physically fit individuals(82). Increases in HR can be the result of decreased vagal activity, increased sympathetic activity, or a combination of these partially independent autonomic pathways(83). Our results indicate relative equivalence of HF-HRV (a vagal measure) and HR (a combined sympathovagal measure) for predicting MRBC mortality, and superior prediction when combined. Thus, the sympathoadrenal pathway likely contributes to reducing survival in the studied cancer patients. Several studies demonstrated relationships between sympathetic activity, the immune system(61, 82, 84), and metastases(85).

Evidence suggests that high HR levels (>100 bpm), may predict shorter survival in cancer and cardiovascular disease(86). Several large-scale studies found that higher HR predicted shorter cancer survival among men(87–90), and also higher HR in combination with lower exercise predicted shorter survival(90). Other studies found no relationship between higher HR and cancer mortality(91–93). Nevertheless, we suggest that a combined measurement of sympathetic and vagal activity may benefit future survival studies.

Evidence in rodents indicates that sympatho-adrenal-medullary system activity, specifically norepinephrine secretion, is associated with vascular endothelial growth factor and blood supply stimulation, and tumor growth(94). This effect was reversed with beta-adrenergic blocker administration. Human and animal models confirm some of those pathways(61, 62,85, 95–100), and several clinical studies have demonstrated that a standard beta-adrenergic blocker, propranolol, is associated with longer breast cancer survival(101–103). To this literature we add evidence that resting HF-HRV/HR, representing the combined influence of increased vagal and decreased sympathetic activity, predicts survival in a clinical sample. This combined measure is easy to assess, potentially giving health-care professionals incremental information on which to base treatment plans.

Limitations

The sample size for this secondary analysis is limited to women with MRBC volunteering to undergo a social-stress test, and was smaller than the larger study powered to test another hypothesis. Replication is necessary for full confidence in this result. Although only disease-free interval differed between the two samples, there may be a selection bias toward less healthy individuals. Our vagal measure indexes efferent vagal activity to the cardiac muscle, and other organs may be differentially innervated by the vagal system depending on local (metabolic) requirements. Also, afferent activity, hypothesized as important to the inflammatory reflex informing the CNS about peripheral inflammation(2), may differ from efferent activity. Despite these limitations, the relationship of HF-HRV with survival indicates that efferent cardiac vagal activity may represent overall afferent and efferent information transfer between the vagal and immune systems and may provide early clinical prognoses in cancer patients.

In sum, our results provide a translational link between basic research on the immunomodulatory function of the vagal system and a clinical population that may be particularly dependent on CNS signalling(85) and responsive to interventions that improve immune function(104, 105). The power of HF-HRV and HF-HRV/HR to predict survival suggests that the autonomic nervous system could be an important target for pharmacological(29), surgical and non-invasive vagus stimulation (106, 107), or behavioral interventions such as HRV and HR biofeedback(30–32), and exercise or insomnia programs(33–36). HF-HRV's predictive power also recommends it as a clinical diagnostic aid in secondary and tertiary prevention measures, and some already suggest that its use would be a prognostic measurement improvement in hospice settings(24).

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Abbreviations

HF-HRV	High Frequency Heart-Rate Variability
HRV	Heart-Rate Variability
HR	Heart Rate
MRBC	Metastatic and Recurrent Breast Cancer
TSST	Trier Social Stress Test
SDNN	Standard deviations of normal-to-normal R-R intervals
HIPAA	Health Insurance Portability and Accountability Act
ECG	Electrocardiogram
METs	Metabolic units
BDI	Beck Depression Inventory
SCID	Structured Clinical Interview for DSM Disorders
MDD	Major Depressive Disorder
PSS	Perceived Stress Scale
MOS-SF 36	Medical Outcomes Study 36-Item Short Form Health Survey
CI s	Confidence Intervals
BMI	Body Mass Index
Bpm	beats per minute
HF-HRV/HR	Combined HF-HRV and HR variable
CNS	Central Nervous System

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Figure 1.

Kaplan-Meier survival curve for lower high-frequency heart-rate variability (HF-HRV) (gold line) versus higher HF-HRV (blue line) from resting baseline data. Censored data is removed from the figure. Breast cancer or cancer was the primary or secondary cause of death for 100% of the patients.

Figure 2.

Kaplan-Meier survival curves for two factors, high-frequency heart-rate variability (HF-HRV) and visceral metastases versus a combined group of bone and chestwall metastases. Figure shows lower HF-HRV with no visceral metastases (solid gold line) versus higher HF-HRV (solid blue line) with no visceral metastasis. Figure also shows lower HF-HRV with visceral metastasis (dashed gold line) versus higher HF-HRV with visceral metastasis (dashed blue line). Censored data is removed from the figure.

Figure 3.

Kaplan-Meier survival curve for a combined measure of high-frequency heart-rate variability and heart rate (HF-HRV/HR), equivalent to standardizing each measure and taking the mean, where the two measures correlate negatively. Lower HF-HRV/HR (gold line) versus higher HF-HRV/HR (blue line) from resting baseline data. Censored data is removed from the figure

Baseline psychosocial, demographic, and medical status variables for metastatic and recurrent breast cancer patients with ($n=87$) and without ($n=16$) HF-HRV data.

Table 1

Measure Psychosocial	HF-HRV Data				No HF-HRV Data				P	Effect Size
	N	Mean or %	SD	N	Mean or %	SD	N	Mean or %		
Beck Depression Inventory	87	11.2	7.8	16	12.6	7.0			0.50	0.18
Depressed? (% Yes)	44/87	50.5		7/12	58.3				0.61	-0.05
Perceived Stress Scale	87	16.7	7.4	16	18.2	6.2			0.45	0.21
Previous Sleep Problems? (% Yes)	34/87	39.1		6/16	37.5				0.91	0.01
Previous Psychiatric Problems? (% Yes)	16/87	18.4		4/16	25.0				0.51	-0.06
Mean Sleep Efficiency	83	0.85	0.10	14	0.83	0.14			0.47	0.21
SF-36 Vitality Scale	83	46.6	23.0	14	47.5	22.5			0.89	0.04
Body Mass Index (kg/m ²)	87	25.0	4.3	16	27.4	6.0			0.057	0.52
METs/day	87	39.6	6.6	11	42.6	9.8			0.34	0.43
Demographic										
Age at Baseline (years)	87	54.2	9.92	16	54.88	8.06			0.81	0.07
Ethnicity (% Caucasian)	67/87	77.0		14/16	87.5				0.51	-0.09
Education									0.79	-0.03
High School Diploma or Below	2	2.3		1	6.3					
Trade School or Some College	32	36.8		4	25.0					
Bachelor's Degree	18	20.7		3	18.8					
Some Graduate School or Master's	31	35.6		8	50.0					
Ph.D., M.D. or J.D.	4	4.6		0	0.0					
Income									0.94	0.003
<\$20,000	4	5.2		2	12.5					
\$20,000-\$39,999	14	18.2		4	25.0					
\$40,000-\$59,999	12	15.6		0	0					
\$60,000-\$79,999	14	18.2		2	12.5					
\$80,000-\$99,999	10	13.0		2	12.5					
\$100,000 or more	23	29.9		6	37.5					

Measure Psychosocial	HF-HRV Data			No HF-HRV Data			P	Effect Size
	N	Mean or %	SD	N	Mean or %	SD		
Medical Status								
Disease-Free Interval (months)	87	53.8	63.26	10	108.90	89.83	0.014 [*]	0.83
Estrogen Receptor Status (% negative)	26/86	30.2		1/10	10.0		0.27	0.14
Site of Metastasis/Recurrence							0.45	−0.06
Chestwall	32	36.8		2	20.0			
Bone	29	23.0		3	30.0			
Viscera	35	40.2		5	50.0			
Treatment (% Yes)								
Surgery	82	94.3		9	90.0		0.49	0.05
Reconstruction	24	27.6		2	20.0		0.99	0.05
Chemotherapy	76	87.4		8	80.0		0.62	0.07
Radiation	72	82.8		6	66.7		0.36	0.12
Hormone Therapy	57	65.5		7	70.0		0.99	−0.03

Note. *p* values reported for Students *t*-test, χ^2 , Cochran-Armitage Trend Test, or Fisher's Exact Tests. Effect Size=Cohen's *d*, Phi Coefficient, or Kendall's τ -c.

* $p < .05$

Table 2

Spearman correlations among possible confounders and HF-HRV ($n=87$).

	HF-HRV	HR	Reconstructive Surgery	Visceral Metastases	Sleep Efficiency
HF-HRV	---				
HR	-0.43**	---			
Reconstructive Surgery	0.23*	-0.16	---		
Visceral Metastases	-0.26*	0.22*	-0.15	---	
Sleep Efficiency	0.30**	-0.24*	0.17	-0.19	---

* $p < .05$,

** $p < .01$