Patterns of Objective Physical Functioning and Perception of Mood and Fatigue in Posttreatment Breast Cancer Patients and Healthy Controls: An Ambulatory Psychophysiological Investigation

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Objective: To monitor objective physiological and self-report measures among apparently disease-free breast cancer patients ($n = 33$) in the first 2 years of posttreatment recovery, using a cross-sectional design, and compare findings with women without histories of cancer or other serious disorders ($n = 33$). Time-since-treatment also served as an independent variable. Few studies have examined adjustment of breast cancer patients after primary treatment or objectively characterized posttreatment, everyday patterns of functioning. **Methods:** A 24-hour ambulatory minute-by-minute cardiorespiratory functioning and accelerometry activity were measured during one day, together with multiple repeated assessments of mood and fatigue. Traditional retrospective measures of well-being were also evaluated. Our ambulatory methodology permitted estimation of physiological rhythms of cardiorespiratory and accelerometry activity. **Results:** Patients reported lower ambulatory levels of energy and poorer mood during the daytime than controls. Time-since-treatment was related directly to both momentary mood and energy as well as to objective measures of activity and respiratory parameters. Retrospective self-reports of impaired mood and symptoms persisted in patients, independently of time-since-treatment and of ambulatory physical or physiological activity. Ambulatory self-report data were associated with concurrent respiratory measures. Chemotherapy-related elevation of heart rate was found but was unrelated to self-report measures. **Conclusions:** Impaired sense of well being based on retrospective measures is not associated with pattern of physical or physiological functioning after treatment for breast cancer. However, ambulatory, momentary levels of mood and fatigue seem to be related to concurrent ventilatory activity and time-since-treatment. This is the first investigation that relates ambulatory and retrospective measures of affect and fatigue to concurrent, real-life physical functioning. **Key words:** breast cancer, heart rate, ecological momentary assessment, depression, fatigue, respiration.

ACCEL = accelerometer activity; F_b = breathing frequency; DC = duty cycle; IF = inspiratory flow rate; T_i = inspiratory time; V_m = minute ventilation volume; RMANOVA = repeated-measures analysis of variance; V_t = tidal volume.

INTRODUCTION

The aftermath of breast cancer and its treatment is prolonged, even when disease interventions are highly successful. Brennan (1) characterized adjustment to cancer as a "long process of adaptation to multiple threats and novel experiences." Sequelae, often lasting years, involve both physiological and psychological symptoms, such as fatigue, depression, anxiety, posttraumatic stress disorder, cognitive impairment, sexual dysfunction, and lymphedema (2–5). Some after-effects may, in turn, be related to the further course of disease and adjustment (6–8). Despite the deleterious, often chronic nature of posttreatment adaptation, even among women who remain free of cancer, there has been relatively little investigation into the relationships between psychological recovery and objective physiological functioning in the

first years after successful cancer treatment (9). Furthermore, we know of no published studies that concurrently examined physiological and subjective psychological processes of posttreatment breast cancer patients during naturalistic, real-life circumstances. Therefore, this study investigates concurrent physiological and momentary self-report measures acquired by means of multichannel ambulatory monitoring during daily life.

Knowledge regarding the relationships between subjective perceived well-being and physiological processes, particularly occurring during everyday life, may help us better to understand and deal with the trajectory of postdisease adjustment as well as potentially offer clues to prediction of further physical or psychological risk. Some important questions include the following: 1) What are the relationships between perceived symptoms, such as fatigue and depressive symptoms, on the one hand, and objective measures of physiological function and patterns of everyday physical activity, on the other? 2) How do patterns of perceived well-being and physiological functioning differ during everyday life between posttreatment breast cancer patients and healthy age- and gender-matched controls? 3) Do physiological and psychological processes manifest similar or distinct time courses of posttreatment recovery? Given indications that posttreatment psychophysiological adaptation may be related to future risk (6,10–13), it would seem important to better characterize the course of recovery—both physiological and psychological—in the immediate months and years after diagnosis and treatment among breast cancer patients who remain free from cancer after treatment.

We compared apparently disease-free women previously diagnosed and treated for breast cancer with an age- and education-matched control group of healthy women who had no history of cancer or any other serious disease. Study

participants were physiologically monitored during everyday life for 24 hours, employing an ambulatory multifunction device that continuously registered accelerometry physical activity, respiration, and the electrocardiogram (ECG). This allowed throughout the day uninterrupted measurements of variations in activity, ventilatory parameters (e.g., respiratory rate, tidal volume (V_t), and minute ventilation volume (V_m), and heart rate (HR). Respiratory measures were chosen because of the well-known posttreatment complaints of dyspnea and objective pulmonary dysfunction among posttreatment breast cancer patients (14–17). The ECG was also recorded due to evidence of anthracycline-chemotherapy-related cardiotoxicity and increased chest pain among posttreatment breast cancer patients (18–20).

Multichannel ambulatory monitoring enabled the assessment of systematic daytime variations of cardiac and respiratory processes across waking hours, potentially of special significance due to findings that aberrant neuroendocrine rhythms are associated with increased risk among posttreatment breast cancer patients (6). We additionally evaluated self-ratings of perceived fatigue, mood state, and type of ongoing activity at 50-minute intervals during awake hours by means of an electronic diary integrated into the ambulatory monitoring device. As previously reported in an earlier paper using this cohort (21), standard psychological inventories were administered that assessed mood, fatigue, depression, and stress levels.

Here we compared, during awake hours, the differences in activity, cardiorespiratory parameters, and subjective electronic diary self-ratings of mood and fatigue between posttreatment breast cancer patients and matched control females. Relationships to previously reported retrospective measures were also examined. Additionally, possible systematic variations in cardiorespiratory activity during the day were evaluated. Furthermore, we examined whether time since completion of primary surgery, chemotherapy, and/or radiation therapy (referred to here as "time since treatment") in the patient sample was associated with levels of activity, physiological functioning, the momentary experience of fatigue and positive and negative mood during the day and evening, or retrospective assessments based on standard self-report inventories. Secondary analyses explored potential relationships to prior chemotherapy, given reports of possible cardiotoxic effects of chemotherapy.

METHODS
Inclusion Criteria
Patients

Inclusion criteria in the breast cancer patient group included: 1) >18 years of age; 2) confirmed diagnosis of breast cancer Stages I-III within the previous 18 months (free of metastatic disease); 3) completion of primary treatment at least 3 months previously (except hormonal therapy); and 4) pre- or postmenopausal status. Women who reported being amenorrheic at least 12 months or reported a surgical menopause were classified as postmenopausal.

Controls

Inclusion criteria for the control group included: 1) >18 years of age; 2) attending the Screen Test program for routine mammography (with negative results); 3) no current or prior diagnosis of any type of cancer; and 4) pre- or postmenopausal status.

Exclusion Criteria

Exclusion criteria for both patients and controls included: 1) concomitant Axis I disorder not in remission (evaluated with a structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision); 2) presence of any of the following medical conditions: diabetes mellitus, previously diagnosed obstructive sleep apnea, pacemakers/defibrillators, atrial fibrillation, myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass graft within 6 months of enrollment, congestive heart failure, uncorrected primary valvular disease, uncorrected thyroid heart disease, renal or hepatic dysfunction, dementia, multiple sclerosis, alcohol or drug abuse within 12 months, current pregnancy, primary sleep disorders including insomnia; 3) medication use that would affect hormone levels or alter autonomic function or sleep including hydrocortisone, anxiolytics, oral contraceptives, hormone replacement therapy, benzodiazepines, nonbenzodiazepine hypnotics, barbiturates, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors. Tamoxifen use was not a contraindication in the breast cancer group due to the high rates of usage in this population.

Recruitment
Patients

Participants were recruited from the Tom Baker Cancer Centre (Calgary, Alberta, Canada). With the approval and cooperation of the breast tumor group staff, eligible patients were invited to participate in the study and given a one-page pamphlet summarizing the research protocol during their clinic visit. If patients were interested in participating, their name was placed on a waiting list administered by the research assistant. Patients were also recruited with pamphlets and posters around the center and they were able to self-refer. The study was approved by the Conjoint Health Research Ethics Board of the University of Calgary Faculty of Medicine and Tom Baker Cancer Centre. Participants were not paid for their participation in the study, but car-parking fees for their laboratory visit were covered.

Controls

Women who were attending for routine mammography screening were recruited after all the patients had been tested. This allowed for selective recruitment to create groups that were similar to the patients in terms of key demographic variables, such as age, menopausal status, and parity. Women were not contacted until after they were aware that their mammogram had come back negative (no cancer present). Women with cancer were also able to refer their eligible friends as control participants, which proved to be a useful strategy to find women matched on important demographic features. Control women were not paid for their participation but they were provided compensation for automobile parking fees.

Data were collected over a period of 11 months.

Measures
Physiological Parameters

The following physiological signals were continuously registered via a multichannel ambulatory monitor (LifeShirt System, Vivometrics, Ventura, California) and stored on flashcards: one channel of ECG (sampled at 200 Hz); two channels of respiration via abdominal and thoracic inductance plethysmography band (50 Hz); and one three-dimensional accelerometer at chest level (50 Hz). We present here only data from awake hours (nighttime data to be separately reported).

Respiratory, cardiac, and accelerometry measures were analyzed by the Vivologic analysis software (Vivometrics), which is a full disclosure analysis system allowing validation of all parameters from the original raw signals. Respiratory parameters included respiratory rate, or breathing frequency (F_b, breaths/minute), inspiratory time (T_i, second), duty cycle (DC, T_i/total cycle time: an index of central nervous system central respiratory timing) (22), V_t (ml), V_m (l/minute), and inspiratory flow rate (IF, l/minute; an index of central

respiratory drive) (22). Previous research has validated this method of ambulatory monitoring of respiratory timing and volumetric parameters (23–28).

Motion activity, also termed physical activity here, was the sum of the three axes of integrated accelerometer signal. On the instrumentation day, we employed a calibration procedure whereby participants walked on an electronic treadmill at three speeds—slow, medium, and fast. The speeds were recorded and the accelerometry data were later calibrated to speed, employing for each individual slow, medium, and fast walking speeds. Between-subject associations of the calibrated and uncalibrated data revealed a correlation of 0.94. Because four participants did not successfully complete the calibration procedure, we report the uncalibrated accelerometry data.

The continuously sampled ECG signal was available for editing in the acquired data. Minute-by-minute HR was computed after all registrations were manually screened for ECG arrhythmias, ectopic activity, and movement artifact in the ECG signal. Minutes with excessive ectopic activity or other artifact in the remaining subjects were removed from all analyses and replaced with interpolated values.

Psychological and Other Self-Report Measures
Ambulatory Electronic Diary Momentary Measures

The LifeShirt system includes a small integrated computer for the digital recording of electronic diary data. A touch screen enables the system to display a computerized dairy questionnaire and momentary self-report data to be regularly entered, at the same time patients are simultaneously physiologically monitored. In this study, monitoring an auditory tone, emitted every 50 minutes during awake hours, signaled participants to complete a standardized, triaged questionnaire. Participants were told to refer to the period immediately before the signal. After practicing completion a few times, the entire questionnaire could be filled out by most people in 1 to 2 minutes. The standardized multiple-choice questions assessed concurrent situation (e.g., at home, at work, or visiting), posture (e.g., sitting, standing, or lying), social situation (e.g., alone, with others), activity (e.g., working, watching TV, or doing sports), level of physical activity (e.g. walking, running, or biking), and subjective perception related to mood (i.e., happy, sad, angry, and anxious) and to fatigue (i.e., level of energy and sense of being worn-out). Subjective mood and fatigue measures were rated on a 10-point Likert scale that was visually represented as a thermometer on the screen. Self-report measures of mood and fatigue are the only items from the ambulatory self-rating scale reported in this article. The three items of negative moods were summed and averaged to provide a single measure of negative mood. Additionally, mood and fatigue measures were often positively skewed and hence transformed to their natural logarithm (ln) to yield normal distributions and to enable application of parametric, repeated-measures analyses of variance (RMANOVAs). However, for ease of interpretation, the untransformed means are provided in the Results.

Retrospective Self-Report Measures

These measures described in a previous publication (21) are reviewed below. In the Results, we provide a summary of those results. Furthermore, only previously unreported findings regarding these measures are presented here.

Stress

Symptoms of Stress Inventory (29) was designed to measure physical, psychological, and behavioral responses to stressful situations.

Depression

The Centre for Epidemiological Studies-Depression Inventory (CES-D) (30) measured depression. A score of 16 has been used extensively as the cut-point for likely clinical depression.

Anxiety

The Spielberger Trait Anxiety Inventory (31) was used to assess trait anxiety.

Mood

The Profile of Mood States (POMS) (32) assesses six affective dimensions: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue inertia, and confusion-bewilderment.

Fatigue

Fatigue was measured by the fatigue subscale of the POMS. Items were "worn-out," "listless," "fatigued," "exhausted," "sluggish," "weary," and "bushed."

Weekly Exercise Questionnaire

The Godin Leisure-Time Exercise Questionnaire was employed to assess average amount of weekly exercise (33). Initial analyses revealed that the total score was correlated with objective measures of average accelerometry activity during awake hours, $r = .36$, $p < .004$ for both groups combined; and $r = .53$, $p < .002$ for the breast cancer patients alone.

Procedures

Participants visited the laboratory on a weekday morning at 8 AM. After providing fully informed consent, they completed questionnaires. They were then connected to the LifeShirt ambulatory monitoring device, and a respiratory calibration of tidal volume was made by having subjects breathe a known volume of air into a closed system for several breaths. Subsequently, the accelerometer physical activity sensor was calibrated by having subjects walk at three speeds on a stationary treadmill. Training then proceeded on how to use the ambulatory electronic diary during awake hours. Subjects returned the next day and were disconnected from the ambulatory monitor. All testing occurred during weekdays.

Data Analysis

Sample size calculations were estimated on the basis of detecting a medium effect size (0.5) between any two variables, with an α of 0.05 and power of 0.80, and it was determined that 29 subjects were needed.

Descriptive statistics were used to describe central tendency (mean, median), and variation (standard deviation, range) of the biological measures in each group. Any values that were significantly skewed were transformed appropriately. A significance value of $p < .05$ was used without correction for multiple comparisons, as these data are exploratory in nature.

Physiological Data

Median values of parameters were calculated for each consecutive minute of daytime and evening hours. The extent of physiological activation is highly dependent on the level of physical exertion (34). Therefore, quintiles of the minute-by-minute accelerometry data were calculated for each subject to characterize five levels of physical activity during the day (i.e., 20% of the day with the lowest level of activity versus 20% with the highest, and all quintiles between). All other physiological measures were then binned according to quintile of physical activity (e.g., average HR during lowest quintile of activity versus during highest quintile of activity).

These data were then also classified into four times of day: 9–11:59 AM, 12–2:59 PM, 3–5:59 PM, and 7–9:59 PM. Thus, for each individual subject, we assessed average physiological data for each quintile of activity for each period of the day (morning, early afternoon, late afternoon, and early evening). In this way, we could examine whether time of day was related to physiological variations controlled for concurrent physical activity. Provided that mean levels of activity for each quintile for each group did not vary as a function of time of day, we could assume that any differences in cardiac or respiratory physiological measures for time of day reflected systematic waking-hour variations. We presumed that such rhythms in specific physiological parameters would occur, and we were interested in determining whether posttreatment cancer patients manifested different patterns of physiological activity than controls across the day.

For each physiological parameter, RMANOVAs with a grouping factor were performed, i.e., group (breast cancer versus controls) × quintile of activity and time of day (the latter two factors repeated measures). Green-

house-Geisser corrections were used for three or more repeated measures. Post hoc comparisons were performed with Tukey tests of honestly significant differences.

To determine the effects of time since primary treatment, we performed correlational analyses within the patient sample to examine associations between time since treatment and physiological measures, each averaged over awake hours. Because we were also interested in possible interactions between time since treatment, time of day and quintile of activity, similar RMANOVAs were performed using below and above 8 months since treatment (median split) and controls as a grouping factor.

Post hoc comparisons within the patient group were also made to examine differences on dependent measures between those having undergone versus not undergone a) chemotherapy, b) radiation therapy, and c) hormone therapy. The specific tests conformed to those previously mentioned, and only significant findings (or the important absence of significance) will be further mentioned.

Self-Report Data

For comparisons of ambulatory self-report parameters between patients and controls, group × time-of-day RMANOVAS were performed. To examine relationships to time since treatment, the same two strategies were used as described above with the physiological data: Correlational analyses were performed between mean levels of the ambulatory self-report measures and time since primary treatment. These were also performed for the retrospective self-report variables. Also, a median split of time since treatment was used as a grouping variable, and RMANOVAs were performed, with time of day as the repeated factor for the ambulatory measures; ANOVAs were calculated for the retrospective parameters.

Physiological Self-Report Associations

Simple Pearson r correlations were calculated between mean physiological levels over waking hours and either retrospective self-report measures or mean ambulatory momentary self-report measures.

RESULTS
Participants

A sample of 33 women in the breast cancer group and 33 in the control group provided data. Demographic characteristics of both groups are presented in Table 1. We found the following: 39% of women with breast cancer were diagnosed with Stage 2 cancer, 33% with Stage 3, and 27% with Stage 1. They were an average of 1.36 (SD, 0.60) years post diagnosis.

TABLE 1. Demographic Data of Breast Cancer Patients and Controls

Variable	Breast Cancer n = 33	Control n = 33
Age[a]	51.25 ± 10.19	53.41 ± 5.98
Body mass index[a]	26.65 ± 5.60	26.68 ± 4.87
Reported weekly exercise[a] (Godin scale units)	32.64 ± 26.19	27.00 ± 25.04
Ethnicity (n, %)		
Caucasian	29 (88)	32 (97)
Other	4 (12)	1 (3)
Education (n, %)		
College+	20 (61)	22 (67)
High school	10 (30)	11 (33)
<High school	3 (9)	0 (0)
Marital status (n, %)		
Married	20 (61)	27 (82)

[a] Mean ± standard deviation.

Twenty-five had received chemotherapy during treatment, and 23 received radiation therapy. Chemotherapy typically included four to six cycles of cyclophosphamide with either doxorubicin or epirubicin, and 5-fluorouracil. Hormone therapy, almost always tamoxifen, was currently being administered in 25 subjects in the cancer group.

Women with breast cancer did not differ from the controls in terms of age, ethnicity, education, marital status, body mass index, or reported levels of weekly exercise (Table 1).

Comparisons Between Breast Cancer Patients and Controls
Psychological and Self-Report Measures
Ambulatory Measures (Figure 1, A–D)

Posttreatment breast cancer patients reported themselves as being less happy ($F(1,53) = 4.87$, $p = .03$) and having less energy ($F(1,53) = 5.96$, $p < .02$) across the day than healthy controls, as well as tending toward more negative affect ($p < .09$). Additionally, there was a time effect across both groups ($F(6.26, 31.70) = 3.84$, $p < .001$, Greenhouse-Geisser corrected), indicating a gradual decrease in energy over the day. No differences between groups occurred on reports of being worn-out. However, once again, there was a prominent main effect of time ($F(5.67,300.96) = 12.00$, $p < .001$), with increasing levels of the sense of being worn-out as the day progressed.

Retrospective Measures

These variables have been previously reported (21). Posttreatment breast cancer patients were more fatigued, depressed, anxious, stressed, and mood-impaired than their match controls, and they reported more somatic and cognitive symptoms. Not previously reported, nine (27%) breast cancer patients and none of the controls showed CES depression scores indicative of clinical depression (scores of ≥16); $\chi^2 = 22.04$, $p < .001$.

Ambulatory Accelerometry and Physiological Measures
Accelerometry Activity

Activity did not differ between groups (Figure 2, A). There were also no interactions between time of day and quintiles of activity. This indicates that the average levels of activity for each quintile were the same for both groups during each of the four phases of the day (i.e., morning, early afternoon, late afternoon, and evening); thus, mean levels of activity within quintiles did not differ as a function of time of day. Therefore, potential interactions for other physiological variables between time of day, quintiles of activity and group are likely to reflect systematic variations in those physiological systems during waking hours.

Respiratory Measures

No significant group effects or group interactions with either quintile of activity or time of day were found. A number of time-of-day effects and interactions between time of day
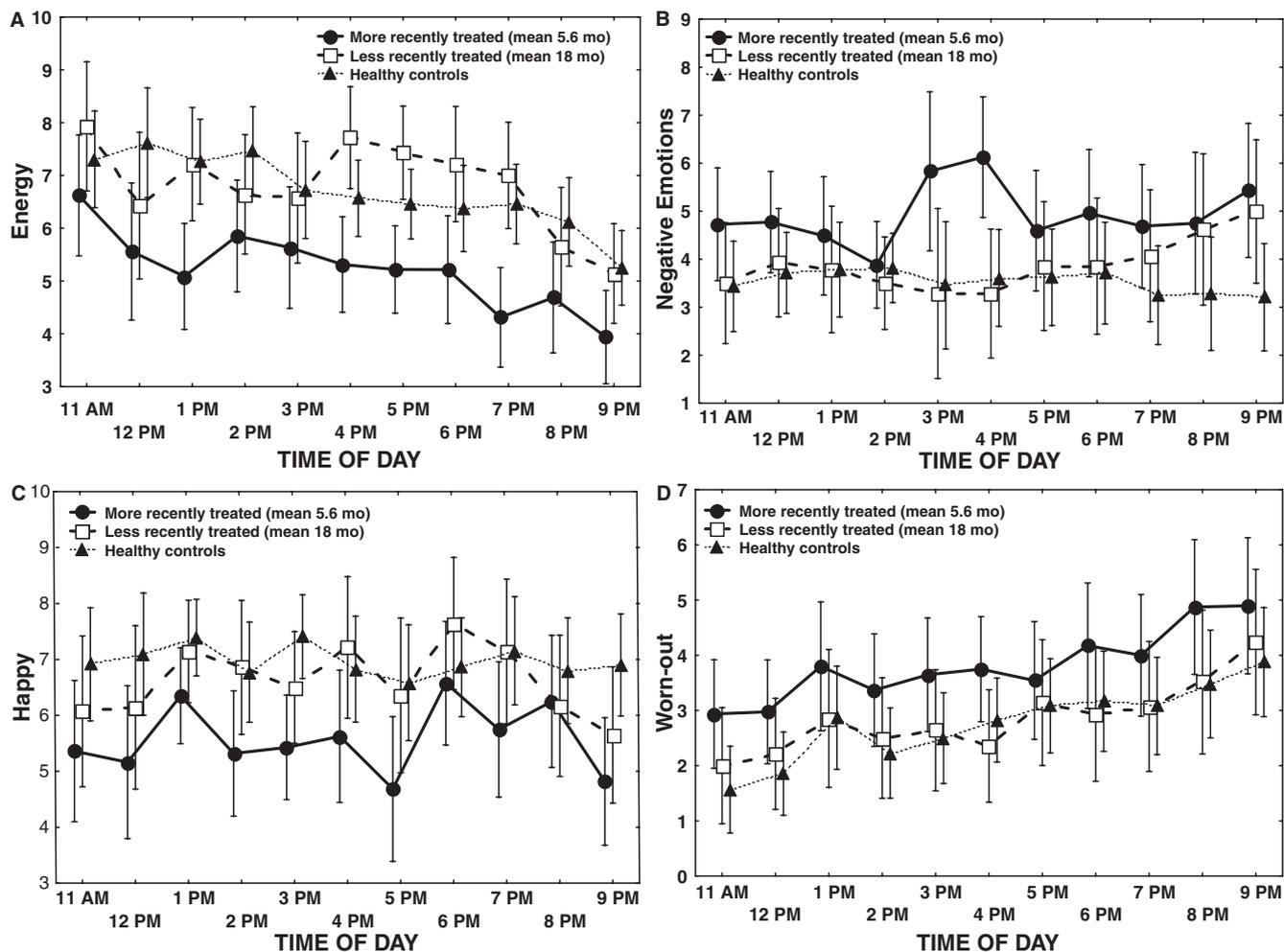
Figure 1. **A–D**. Momentary self-report measures in relationship to time since treatment and time of day (whiskers represent 95% Confidence Interval).

and quintile of activity were significant for respiratory variables (all <.01). In general, respiratory activity was attenuated during the morning hours and at relatively similar levels at other times of day; interactions indicated that this pattern was more evident at sedentary quintiles of activity than during quintiles indicating greater exertion, thus paralleling cardiac variations to time of day and activity level. Thus, respiratory rate and DC were decreased and V_t was elevated during low levels of physical activity during the morning. However, these effects did not distinguish between groups.

Heart Rate (Figure 2, B)

HR was greater for women with breast cancer than controls throughout the day (group effect: $F(1,53) = 12.899$, $p < .001$). HR also showed a significant time-of-day × quintile-of-activity effect (corrected $p < .02$), in which morning HR was lower than during other times of day; these effects were most marked during the lowest two quintiles of physical activity.

Cardiac Relationships to Chemotherapy

Patients were grouped according to those who had and those who had not undergone chemotherapy. The two groups

were compared with each other and with healthy controls (three groups instead of two), and the above-mentioned analyses were repeated. Significant group effects were found for HR ($F(2,52) = 11.72$, $p < .001$) (Figure 2, B). HR was substantially higher for patients who had undergone chemotherapy, as compared with the other two groups (about 12 beats/minute across the day). Post hoc analyses revealed no differences between controls and patients who had not undergone chemotherapy. We also performed analyses on the accelerometer data to evaluate whether differences in physical activity level during the day may have accounted for group variations in HR. There were no main or interactive group effects for any other variable reflecting differences between patients with and without chemotherapy. When the same analyses were repeated with patients separated into radiotherapy and no radiotherapy groups, there were no effects for radiotherapy. Similarly, HR variations were not related to ongoing hormone therapy.

Correlations Between Physiological and Self-Report Measures

Retrospective measures were not significantly correlated with any physiological parameter for comparisons when pa-
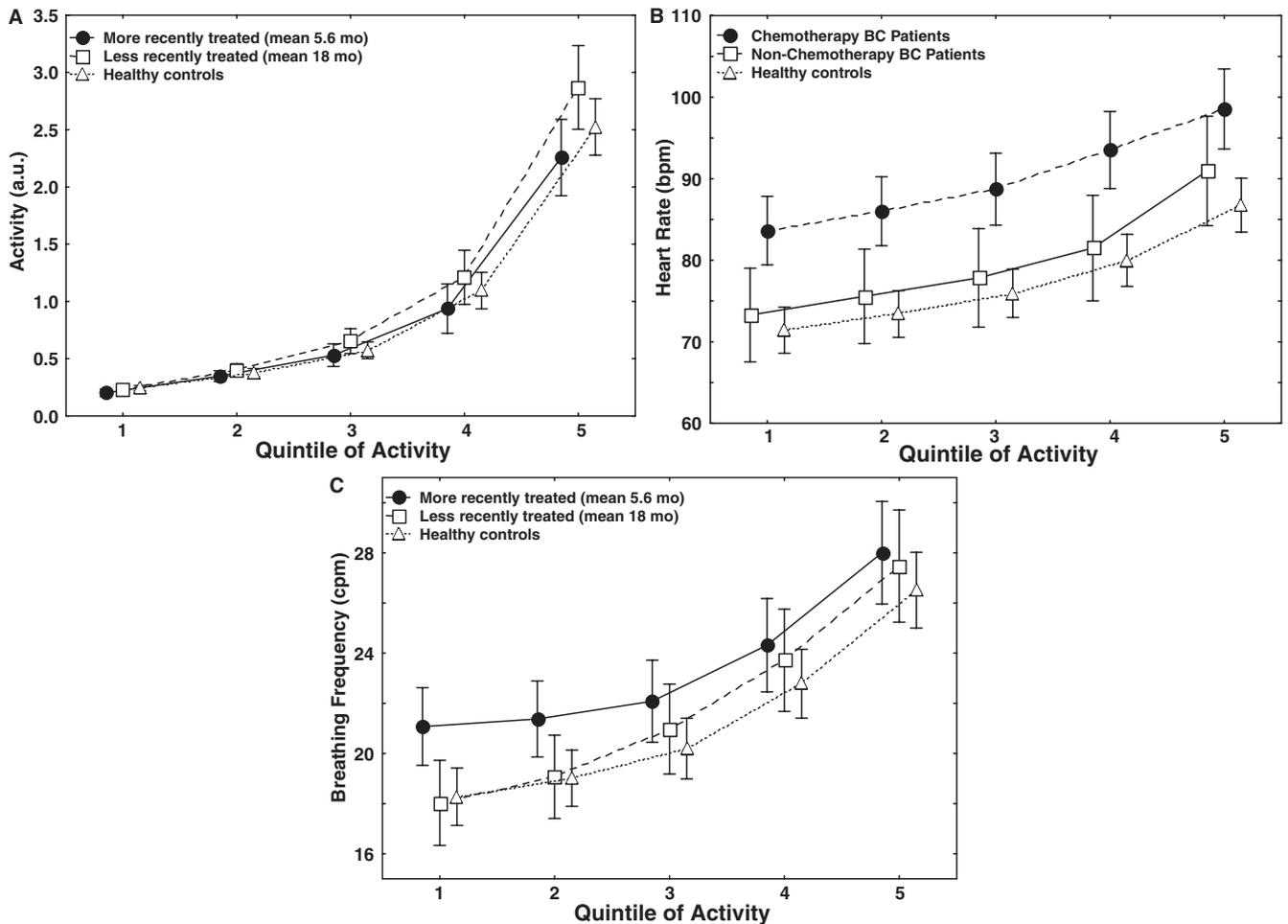
Figure 2. **A–C** Activity (arbitrary units), heart rate, and respiratory rate related to quintile of awake activity (whiskers represent 95% Confidence Interval). **A** and **C** are presented as a function of time since treatment; **B** is presented as a function of having undergone chemotherapy or not.

TABLE 2. Correlations Between Mean Levels of Momentary Self-Rating Variables, and Respiratory and Activity Measures (Breast Cancer Patients Only)

	F_b	IF	DC	V_m	V_t	ACCEL
Worn-out	0.12	−0.39*	0.33**	−0.30	−0.39*	−0.21
Negative affect	−0.04	−0.51*	0.13	−0.47*	−0.49*	−0.21
Happiness	0.12	0.46*	−0.12	0.42*	0.40*	0.39*
Energy	−0.03	0.36*	−0.36*	0.29	0.33**	0.37*

F_b = breathing frequency; IF = inspiratory flow rate; DC = duty cycle; V_m = minute ventilation; V_t = tidal volume; ACCEL = accelerometry activity.
* $p < .05$; ** $p < .10$.

tients and controls were pooled. However, mean IF during awake hours was significantly positively associated with mean levels of all momentary self-report measures ($p < .05$), positively for happiness and energy ($r = .29$ and $.40$, respectively), and negatively for negative affect and sense of being worn-out (both $r = .27$). Similar patterns were found for V_t and V_m, which can be attributed to the large correlations between IF and the latter measures ($r > .9$). Averaged accelerometry activity was also correlated with mean self-reported energy ($r = .41$) and happiness ($r = .28$) across the pooled sample. No associations were found between HR and any momentary self-report measures.

The same analyses for the breast cancer patients alone also revealed a similar pattern: retrospective measures were unrelated to any physiological parameters. Nevertheless, there was a consistent pattern of significant or near-significant associations between averaged momentary ratings across the day and mean levels of respiratory parameters (Table 2); particularly volume-related variables of IF and V_t were correlated with ambulatory self-report measures. Also, associations were found between mean activity and both energy and happiness. There was no association between the amount of weekly exercise and any of the momentary self-report variables. Again, mean HR did not correlate with any self-report measure.

TABLE 3. Momentary Ratings of Mood and Fatigue During Ambulatory Monitoring

	More Recent BC Means (95% CI)	Less Recent BC Means (95% CI)	Controls Means (95% CI)
Ambulatory			
Happy	5.57 (4.70–6.45)	6.62 (5.64–7.62)	6.97 (6.47–7.47)
Negative emotions	6.34 (4.14–8.55)	4.87 (4.07–5.67)	4.65 (4.21–5.08)
Energy	5.22 (4.41–6.03)	6.81 (5.79–7.84)	6.69 (6.28–7.10)
Worn-out	3.82 (2.75–4.88)	2.86 (1.97–3.75)	(2.26–3.29)

BC = breast cancer; CI = Confidence Interval.

Analyses Related to Time Since Treatment

Three groups, patients <8months and >8 months since treatment (based on a median split) and controls, were also analyzed for all self-report and physiological variables repeating steps of preceding RMANOVAs. Means, standard deviations, and ranges of groups with briefer and longer durations since treatment were 5.57 ± 1.92 months (51–240 days) versus 16 ± 4.60 months (277–704 days), respectively. Time since diagnosis was 11.82 ± 3.49 months versus 21.70 ± 6.90 months.

Psychological and Self-Report Measures
Ambulatory Measures (Figure 1 and Table 3)

Time since treatment was significantly associated with mean momentary levels of self-reported negative affect, happiness, and energy ($r = -.39, .36,$ and $.42$, respectively) and approached significance for sense of being worn-out ($r = -.32, p < .09$). These effects were also reflected in the median-split RMANOVA group effects for energy across the day ($F(2,52) = 6.80, p < .003$) and happiness $F(2,52) = 4.44, p < .02$), with a group × time interaction effect for negative emotions ($F(12.7,330.9) = 2.33, p < .006$). Post hoc tests indicated that more recently treated women reported less energy and were less happy, in general, than less recently treated women, with no differences between the latter group and controls. Post hoc analyses for negative affect indicated that both breast cancer groups showed heightened levels of negative affect during evening hours, in comparison with controls. Furthermore, more recently treated patients reported elevated levels of negative emotion during late afternoon in contrast to both other groups.

Retrospective Measures

Correlational analyses examining associations time since treatment and retrospective self-report data indicated that more recently treated patients did not differ, or tend to differ, from less recently treated patients on any retrospective ratings of well-being or symptoms.

Ambulatory Accelerometry and Physiological Measures
Accelerometry Activity (Figure 2, A)

Mean activity during awake hours was related to time since treatment ($r = .37$). The median-split RMANOVA analyses also revealed significant group effect ($F(2,61) = 3.43, p < .04$), and there was also a group × quintile effect ($F(2.7,81.9) = 3.27, p < .03$). Post hoc tests indicated that more recently treated patients manifested lower levels of activity than less recently treated patients and controls. This was most apparent during the 20% of the day in which participants were most active (i.e., the highest quintile) and not apparent during the most sedentary quintiles (Figure 2, A).

Respiratory Measures

Average IF and V_t during awake hours were positively related to time since treatment ($r = .37$ and $.41$, respectively). In regard to the median-split analyses, an effect of group × quintile was found for respiratory rate ($F(3.3,101,3) = 2.85, p < .04$). Respiratory rate (Figure 2, B) was higher for more recently treated patients during the most sedentary two quintiles of the day, in comparison with both less recently treated patients and controls. No other group effects were significant.

Heart Rate

HR did not reveal distinct patterns of differences between less recently and more recently treated patients or between either of these groups and controls. Thus, time since treatment did not seem to independently influence cardiac measures.

DISCUSSION

The goal of this study was to characterize, within a cross-sectional design, a range of objective physiological and self-report measures among apparently disease-free breast cancer patients during the first 2 years of recovery after primary treatment, as well as to compare findings with a carefully matched sample of healthy women with no history of cancer or other serious disorders. Time from primary treatment was also used to evaluate effects of recovery over the posttreatment period, ranging from 52 to 704 days. We examined minute-by-minute cardiorespiratory functioning and accelerometry activity, together with multiple momentary assessments of mood and fatigue during naturalistic conditions of a single day. We also performed additional analyses of traditional retrospective measures of affect and well-being partially reported elsewhere (21). Our ambulatory methodology permitted estimation of rhythms, or at least systematic variations, of respiratory, cardiac, and accelerometry parameters, related to time of day, during awake hours. This investigation is the first to relate both ambulatory and retrospective measures of affect and fatigue to concurrent and real-life physical functioning.

Comparisons Between Patients and Controls

Results from the ambulatory diaries of momentary experience indicated that patients reported themselves to be less happy, have less energy, and be more prone to negative emotions across the day than control subjects. These findings are consistent with retrospective differences reported earlier (21), in which negative mood and elevated symptom reporting was more pronounced in the patient group.

In the current analyses, breast cancer patients—in contrast to controls—did not demonstrate different levels of activity across the day or show lower mean levels of activity during quintiles of greatest physical exertion, despite patients reporting themselves to be more fatigued than controls, as indicated by diminished energy and heightened sense of being worn-out. Also, no ventilatory parameters distinguished between patients and controls.

The most pronounced physiological effect was the substantially and continuously elevated HR among breast cancer patients in contrast to controls. Secondary comparisons of patients treated with chemotherapy versus controls and patients not having undergone chemotherapy indicated that only the chemotherapy group manifested cardiac hyperactivity, the effects being very significant despite a relatively small sample size. A 12 beat/minute elevation, in comparison to controls, was found among patients treated with chemotherapy across the day. These effects were unrelated to exposure to radiotherapy or to hormone therapy. Because almost all patients treated with chemotherapy received anthracycline therapy, it would seem plausible that this form of chemotherapy may produce subclinical cardiotoxicity—either affecting the heart itself or neural pathways—that has thus far gone undetected. Nevertheless, and especially because of our small sample size, this hypothesis warrants careful further investigation and confirmation.

Respiratory and cardiac parameters did exhibit apparent systematic variations across waking hours that could not be accounted for by variations in the level of physical activity: Cardiac and respiratory function characteristically seemed relatively quiescent in the morning. Nevertheless, physiological findings did not suggest any differences in daytime autonomic rhythms between breast cancer patients and controls. The lack of difference in systematic physiological variations is consistent with previously presented cortisol data (21) and may differ from other studies due to the fact that our sample comprised Stage 1 to 3 breast cancer patients apparently in remission.

Associations Between Physiological and Self-Report Measures

HR was not significantly correlated with any retrospective or momentary self-rated measure. This provides additional support to the notion that chemotherapy-induced subclinical cardiotoxicity may be the cause of elevated levels of HR in chemotherapy-treated breast cancer patients.

Respiratory parameters, averaged over awake hours, were also not associated with retrospective self-report measures but were significantly related to each of the momentary self-report parameters when patients and controls were pooled. The correlations remained significant when analyses were performed only for the patient group. Volume-related parameters provided a very consistent picture: IF was directly related to both positive items (energy and happiness) and negatively related to both items reflecting poorer functioning (sense of being worn-out and negative affect); V_t and V_m provided very

similar effects. These associations suggest that brain centers responsible for respiratory drive, indexed by IF (22), may be related to mood and symptom perception in everyday life. On the other hand, parameters representing central control of temporal aspects of the breathing pattern, such as DC and f_b, were less prominently related to ambulatory self-report measures, with only DC significantly associated with self-reported energy among the patient group.

The precise meaning of these associations between ventilation and momentary well being is unclear. To the best of our knowledge, this is the first investigation of ambulatory respiratory-mood/symptom relationships during everyday life, and further study is necessary to replicate these findings. It has long been recognized that respiratory parameters are often tightly linked to facets of well-being (22–25), and our findings may reflect this relationship. However, most studies have examined relationships between breathing and well being under sedentary conditions or situations in which levels of ventilation and metabolic activity dissociate (e.g., hyperventilation) (22,23). Under those circumstances, increased ventilation is often associated with negative, and not positive, affect, as we found. On the other hand, we monitored breathing during normal daily life, typically under highly varied levels of activity. Volumetric parameters of breathing are particularly related to metabolic activity (34). Therefore, it is possible that variations in physical fitness primarily mediate associations between momentary self-report measures and ventilation. However, the fact that reported exercise frequency was not significantly correlated with any of the momentary measures of mood or fatigue militates against this explanation. Thus, these findings may suggest that ventilatory parameters are differently related to well-being in and out of the laboratory, possibly indicating that more robust breathing during varied activities reflects enhanced sense of well-being, or conversely depressed ventilation mirrors depressed affect.

Whatever the explanation for associations between ventilatory parameters and self-report measures of mood and fatigue, it is noteworthy that they were only found for the ambulatory measures and not the retrospective ones. These results suggest that time proximity may play a significant role in the strength of relationships between physiological activity, on the one hand, and psychological and symptom perception, on the other.

Relationships to Time Since Primary Treatment

The most recently treated patients manifested greatest impairment of momentary mood and energy levels, and the less recently treated women were often similar to the healthy comparison group. Nevertheless, retrospective questionnaires of well-being and symptoms indicated no significant or even marginal effects for time since treatment. Hence, patients, in contrast to controls, continued to show sometimes serious impairments in retrospective psychological and physical complaints that were unrelated to time free of treatment. For example, over one quarter of the breast cancer patients scored above the accepted threshold for likely serious depression versus no one in the control group, and this was not associated

with time since treatment. Why standardized retrospective measures and ambulatory self-ratings are discrepant is unclear, but may relate to a distinction between momentary experiences of well being as opposed to more generalized and less specific recall of recent moods and symptoms. In any case, these data suggest that momentary measures of fatigue and well-being may be more sensitive to such factors as phase of recovery than retrospective inventories.

Average accelerometer activity during awake hours was associated with time since treatment. In analyses employing a median split of time since treatment, more recently treated patients showed attenuated levels of activity during the quintile of greatest activity. Activity was also positively associated with levels of reported energy among patients. Interestingly, averaged ambulatory energy ratings were related to time since treatment, and sense of being worn-out showed a marginally significant effect. However, there was no association between retrospectively assessed fatigue and time since treatment, nor were variations in POMS fatigue related to any objective measures of physiology or activity. These results may suggest that retrospective and momentary assessments of fatigue also reflect at least partially different phenomena.

Average IF and V_t during awake hours were positively related to time since treatment. Additionally, sedentary respiratory rate was related to posttreatment recovery among breast cancer patients: more recently treated patients also showed higher resting respiratory rates than controls or less recently treated patients in the RMANOVAs employing a median split of time since treatment as a grouping variable. This provides some support for the possibility that elevated dyspnea and other cardiopulmonary complaints among breast cancer patients (21) may be associated with objective ventilatory activity.

It should also be noted that, although systematic variations in physiological activity unrelated to levels of metabolic activity did occur as a function of time of day, there were no differences between more and less recently treated patients, suggesting similar patterns of daytime autonomic rhythms among both groups.

One general conclusion based on these results is that cardiorespiratory physiology and activity pattern are not closely related to retrospective ratings of well being or symptoms. These findings suggest that traditional retrospective assessments of psychological and symptomatic adjustment to cancer and its treatment over the first years of recovery are generally independent of physiological factors in female breast cancer patients. A recent 4-year follow-up study of women treated for early-stage breast cancer found no relationship between depressive symptoms and objective cancer-related symptoms, such as cancer stage, type of treatment, or tamoxifen use (35). Our own study shows that posttreatment patients may be as active as others in daily life but still are more likely to suffer from psychological distress and symptoms.

Mean levels of ambulatory mood and fatigue over the day did correlate with variations of respiratory parameters, particularly those related to central respiratory drive. Based on these preliminary findings, it may be important to explore concurrent relationships between respiratory measures and both mood and physical symptoms in real-life settings. Furthermore, it would seem valuable to investigate retrospective self-ratings of affect and symptoms in relationship to both physical fitness and real-life ambulatory psychophysiological data. Such research would help us to determine the extent to which physical fitness may mediate associations among physiological measures and general (retrospective) and more immediate (momentary) indices of well-being in health and disease. These relationships may have important implication for further development of long-term rehabilitation programs for recovering breast cancer patients.

A number of limitations and strengths of the present investigation should be mentioned. First, we cannot be sure that other physiological parameters besides those monitored might have provided different and meaningful information. Our sample was also small, and the single day of ambulatory monitoring may have been insufficient to provide fully reliable information about patterns of activity and physiological functioning during daily life. Some of our analyses employed a median split of time since primary treatment as a grouping variable to explore interactions with time of day and/or activity level. Although the split resulted in a relatively meaningful division of shorter and longer durations (2–8 months versus 9–24 months), this distinction remains arbitrary and determined by our sample characteristics.

Our findings, nevertheless, demonstrate the feasibility of naturalistic psychophysiological monitoring in cancer patients. We have shown it is possible to characterize patterns of activity and physiological functioning across the day, and we provide a method by which rhythms of physiological activity under naturalistic conditions can be determined without being confounded by variations in physical activity. Furthermore, we also studied a relatively homogeneous group of successfully treated and apparently disease-free breast cancer patients and examined a circumscribed period of posttreatment recovery that may be critical to the later psychosocial adjustment of breast cancer patients. Finally, our findings, focusing on objective physical measures and both traditional retrospective and momentary assessments of well-being, clearly point to the importance of complementary medical and psychosocial strategies for supporting posttreatment cancer patients.

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