Adrenal Hormone and Metabolic Biomarker Responses to 30 min of Intermittent Cycling Exercise in Breast Cancer Survivors

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Abstract

The aim of this study was to explore the effect of one bout of aerobic exercise on epinephrine, norepinephrine, cortisol, glucose, lactate, and free fatty acid (FFA) responses in breast cancer survivors and healthy controls. 9 female breast cancer survivors and 9 women without a history of cancer completed 30 min of cycle ergometry exercise at 60 % of VO_{2peak}. Blood samples were taken pre-exercise, immediately post-exercise, and 2 h post-exercise from which plasma concentrations of study variables were measured. Immediately and 2 h post-exercise, increases were observed in epinephrine (control group only) norepinephrine (both groups), lactate (both groups), and FFA (both groups immediately post-exercise; breast cancer survivor group only at 2 h post-exercise) ($p < 0.05$). Cortisol decreased immediately and 2 h post-exercise in the control group while glucose decreased immediately post-exercise in the breast cancer survivor group ($p < 0.05$). In conclusion, breast cancer survivors appeared to display attenuated epinephrine, cortisol, and lactate responses while displaying larger magnitude changes in glucose and FFA responses compared to controls. These preliminary findings may have implications for the regulation of metabolism during exercise in breast cancer survivors.

Keywords

acute aerobic exercise; stress hormones; energy metabolism; oncology patients

Introduction

The American Cancer Society has estimated that there are over 2.8 million breast cancer survivors alive in the United States [American Cancer Society, What are the key statistics

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about breast cancer? (February 22, 2016). On the Internet: http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistics; (April 26, 2016)]. Major cancer treatment can affect virtually all of the body's physiological systems, causing significant physical and psychological distress that may persist for months or years after the completion of therapy [26]. Over the past 2 decades, numerous studies have investigated the impact of exercise training on physical functioning in breast cancer patients and survivors [17, 23, 24]. The primary endpoint of many of these investigations was the effect of exercise training on cardiorespiratory capacity. Other outcomes have also been addressed, including changes in muscular strength, body composition, functional quality of life, fatigue, anxiety, and self-esteem [24].

In recent years, studies examining the impact of aerobic exercise on endocrine parameters in cancer patients have emerged [8, 12, 15, 16, 21, 22, 25, 27, 32, 36, 38]. These studies suggest that beneficial changes in hormone levels after aerobic exercise training may be associated with favorable outcomes including decreased stress and decreased risk for developing cardiovascular or metabolic disease [22,25]. These findings are pertinent, as cancer survivors may be at a higher risk for developing comorbid conditions including cardiovascular disease [22,25]. Additionally, examining the impact of aerobic exercise on the endocrine system in cancer patients and survivors may be important because of the role of adrenal hormones in mediating immune responses that are associated with anti-cancer defense [13].

The hormones of the adrenal gland, namely the catecholamines (epinephrine and norepinephrine) and cortisol, may be especially important to study because their release is dependent on exercise intensity and duration, and because of their widespread physiological effects, particularly regarding energy metabolism. In healthy individuals, catecholamine and cortisol levels rise proportionally with respect to exercise intensity and duration. They elicit a wide array of metabolic responses, targeting organs such as the skeletal muscle, adipose tissue, liver, and pancreas [30,31]. In response to these hormones, free fatty acids are released from stores in the skeletal muscle and adipose tissue and are the primary energy substrate utilized during low- and moderate-intensity exercise, while glucose is released from stores in the liver and skeletal muscle to provide energy especially during high intensity exercise [30, 31]. For breast cancer survivors however, energy substrate utilization during aerobic exercise appears to differ from those of healthy individuals. Evans et al. [11] and Tosti et al. [40] found that blood lactate levels (a product of glucose metabolism) were significantly lower in breast cancer survivors compared to physically similar healthy controls across various aerobic exercise intensities. Furthermore, Tosti et al. [40] observed that as exercise intensity increased, fat oxidation rates were significantly higher and carbohydrate oxidation rates were significantly lower in breast cancer survivors compared to healthy controls. The exact mechanisms driving these differing responses are unclear but could be related to cancer-associated endocrine changes in glucose and free fatty acid metabolism. It is possible that certain breast cancer treatments may lead to deregulation in adrenal gland hormone release and hypothalamic-pituitary-adrenal (HPA) axis function [4,14,34]. Therefore, it is plausible that hormonal release during acute aerobic exercise could be altered in breast cancer survivors during acute aerobic exercise, although such studies are extremely scarce.

Current exercise guidelines put forth by the American College of Sports Medicine for cancer patients and survivors are very similar to those for the general population [35]. In order to construct the most relevant and specific aerobic exercise guidelines for breast cancer patients and survivors, it is important to understand how the body's physiological systems respond to and recover from acute exercise. This is particularly important for systems such as the endocrine system and metabolism, where exercise responses in the cancer patient population and comparisons to exercise responses of healthy individuals have not been extensively studied. Understanding how adrenal gland hormones respond to and recover from acute aerobic exercise as well as their relationship with metabolic responses can further aid researchers and clinicians in constructing the most precise exercise prescriptions, thus allowing a cancer patient or survivor to reap the maximum health benefits of exercise. Therefore, the purpose of this study was to compare the catecholamine, cortisol, free fatty acid, glucose, and lactate responses to an acute bout of moderate-intensity intermittent exercise in breast cancer survivors and healthy controls. Whereas the previous studies by Evans et al. [11] and Tosti et al. [40] show that some aspects of glucose and fat metabolism appear to differ between breast cancer survivors and physically similar healthy controls, they did not investigate physiological mechanisms. Therefore, this current study aimed to expand the metabolic profile that was examined and to explore if changes in free fatty acid, glucose, and lactate levels may be driven by the neuro-endocrine responses of the catecholamines and cortisol.

Materials and Methods

Subjects

The participants who took part in this study have been previously described [10]. Briefly, women who were survivors of Stage I–III invasive breast cancer and women who had never been diagnosed with or treated for cancer were included in this study. All subjects were between the ages of 40–70 years, were not regular users of anti-inflammatory medications, and had not experienced a menstrual period for approximately 1 year prior to enrollment. Inclusion in the breast cancer survivor group further required that subjects had received chemotherapy and had completed all planned surgery, chemotherapy, and radiation therapy 3–6 months prior to enrollment. Inclusion in the control group further required that subjects were sedentary and were free from cardiovascular and musculoskeletal disease that would render aerobic exercise participation unsafe. Subjects were recruited from the University of North Carolina at Chapel Hill (UNC-Chapel Hill) and the surrounding areas after obtaining approval from the Protocol Review Committee at the Lineberger Comprehensive Cancer Center and the institutional review boards in the Department of Exercise and Sport Science and School of Medicine at UNC-Chapel Hill. All aspects of this study were con-ducted according to the ethical standards as required for publication [19].

General procedures

Each subject completed 3 laboratory visits during the course of the study. During visit 1, subjects were introduced to the study, signed all IRB-approved written informed consent documents, received a comprehensive medical and physical screening, and completed a peak oxygen uptake test (VO_{2peak}) on the cycle ergometer to assess maximal aerobic power [10].

During visit 2, subjects completed a 30-min exercise bout on the cycle ergometer at a workload corresponding to 60 % of VO_{2peak}. Blood samples were obtained immediately pre-exercise, immediately post-exercise, and 2 h post-exercise. During visit 3, one resting blood sample was obtained at 24 h post-exercise. Before each visit, all subjects were asked to follow a set of pre-assessment guidelines, which included the following: no eating for at least 2 h prior to testing, no exercise for at least 12 h prior to testing, maintaining adequate hydration, no caffeine for at least 12 h prior to testing, and no alcohol use for at least 48 h prior to testing. All testing took place in the laboratory facilities housed within the Department of Exercise and Sport Science at the UNC Chapel Hill.

Visit 1: Medical/physical screening and VO_{2peak} test

Subjects completed a comprehensive medical history questionnaire, underwent a 12-lead resting electrocardiogram (ECG) and a physical examination to determine if they were healthy enough to take part in the study testing procedures [33]. After subjects were cleared for participation, height and body mass were measured using a portable stadiometer (Perspective Enterprises, Portage, Michigan, USA) and a calibrated balance-beam scale (Detecto, Webb City, Missouri, USA). Body mass index (BMI) was calculated from height and body mass. Percent body fat was assessed using a Discovery dual-energy X-ray absorptiometry (DEXA) scanner (Hologic, Inc., Bedford, Massachusetts, USA). For subjects in the breast cancer survivor group, details of their cancer treatments were recorded to include surgery type, chemotherapy medications received, whether or not radiation therapy was received, and the use of other medications relevant to the cancer treatment.

Subjects then performed the Åstrand Cycle Ergometer Maximal Test protocol to measure VO_{2peak} [2]. The test was performed on a Lode electronically-braked cycle ergometer (Lode, Gronigen, The Netherlands). Subjects began by pedaling at a workload of 50 watts for 3 min and then progressed by increments of 25 watts every 3 min until volitional fatigue. Heart rate and rating of perceived exertion (RPE) [3] were recorded at the end of every minute of the test. Expired gases were collected and analyzed using a TrueMax 2400 Metabolic System (Parvo Medics, Salt Lake City, Utah, USA). Minute-by-minute heart rates were obtained from 12-lead ECG monitoring (GE CASE Cardiosoft V. 6.6 ECG diagnostic system, General Electric, Palatine, Illinois, USA). VO_{2peak} was the highest VO_2 measured by the metabolic system during the last stage of the test. Peak workload was the workload on the cycle ergometer that corresponded to the subject's VO_{2peak}. Once the test was complete, subjects cooled down by pedaling at a very light workload. Monitoring of vitals continued for at least 5 min post-exercise and until heart rate and blood pressure had returned to near-baseline levels [5]. Results of the Åstrand test were used to calculate the submaximal workload that subjects would be performing during visit 2.

Visit 2: Intermittent cycling trial

The exercise trial began between 7:00–10:00 am in order to control for daily variations in hormonal levels. Subjects performed an acute bout of exercise on the cycle ergometer at a workload corresponding to 60% of the subject's VO_{2peak}. This intensity is commonly used in studies that examine the effects of aerobic exercise on physical functioning, as well as training, in breast cancer patients [24,35]. Previous pilot testing with recent breast cancer

survivors demonstrated that most were unable to complete the 30-min bout of continuous exercise. Therefore, in order to ensure that all subjects would be able to complete the exercise session and maintain the desired intensity, an intermittent protocol was employed with alternating ten, 3-min intervals of exercise with 1.5 min of rest, for a total of 30 min of exercise in a 43.5-min period.

At the beginning of the laboratory visit, an angiocatheter was placed in an antecubital vein in the arm for the purpose of blood sampling. The catheter was kept patent by a sterile saline solution. Subjects then rested in the supine position for approximately 20 min. A pre-exercise blood sample was drawn into two 3-mL K_3EDTA Vacutainer® tubes. Subjects then sat quietly on the cycle ergometer for 3 min while pre-exercise metabolic data was collected. Subjects were then allowed to warm up for 4–5 min, which included cycling and stretching. Afterwards, subjects performed the exercise bout at the workload that corresponded to 60 % of VO_{2peak}. Expired gases were monitored during the first, third, seventh, and tenth exercise interval. Workload was adjusted as needed in order to ensure that subjects maintained an exercise intensity as close as possible to 60 % of VO_{2peak}. Heart rate and RPE were recorded every 3 min. When the exercise bout was complete, subjects immediately dismounted the cycler ergometer and returned to the supine position. An immediate post-exercise blood sample was drawn into Vacutainer® tubes, with sterile saline injected to keep the catheter patent.

For the remainder of the visit, subjects rested in the laboratory. Subjects were not allowed to ingest any food or beverage with the exception of water. At 2 h post-exercise, another blood sample was obtained in the same manner as previously described. The angiocatheter was removed and any necessary bandaging was performed.

Visit 3: 24-h follow-up session

Subjects returned to the laboratory 24 h after completion of the exercise session to obtain a resting blood sample. Blood was sampled from an antecubital vein in the arm.

Standard venipuncture technique was used to draw the blood into 2 Vacutainer® tubes.

Perceived stress scale

At the beginning of visits 2 and 3, subjects were asked to complete the Perceived Stress Scale (PSS), which is a widely-used instrument for measuring the perception of stress [6,7]. The PSS is a 10-item questionnaire in which scores may range from 0–40, with higher scores denoting higher levels of stress. The PSS was administered to assess subjects' perceptions of the stressors in their daily life because these stressors could potentially impact resting values of catecholamines and cortisol.

Determination of plasma levels of adrenal hormones and metabolic biomarkers

Whole blood samples were centrifuged at 4 °C at 3 000 rpm for 10 min using an IEC Centra-8R refrigerated centrifuge (International Equipment Company, Needham Heights, Massachusetts, USA). The plasma portion was isolated and stored in vials at – 80 °C until the time of analysis. Epinephrine, norepinephrine, and cortisol were measured using

enzyme-linked immunosorbent assay (ELISA) kits (Abnova, Taipei City, Taiwan). The epinephrine assay had an analytical sensitivity of 10 pg/mL, mean intra-assay coefficients of variation of 6.9–15.8 %, and mean inter-assay coefficients of variation of 13.2–18.2 %. The norepinephrine assay had an analytical sensitivity of 50 pg/mL, mean intra-assay coefficients of variation of 9.8–16.1 %, and mean inter-assay coefficients of variation of 8.5–15.0 %. The cortisol assay had an analytical sensitivity of 0.44 ng/mL, mean intra-assay coefficients of variation of 6.2–9.4 %, and mean inter-assay coefficients of variation 8.6–15.0 %.

Free fatty acid levels were also measured using an ELISA kit (Wako Diagnostics, Richmond, Virginia, USA). The FFA assay had an analytical sensitivity of 0.0014 mEq/L, intra-assay coefficients of variation of 0.61–0.75 %, and inter-assay coefficients of variation of 0.75–4.91 %. Glucose and lactate were measured using a DT60 Johnson & Johnson automated blood analyzer (Rochester, New York, USA). All samples were run in duplicate with the exception of the epinephrine and norepinephrine assays, in which samples from 2 control subjects were run in single due to limited plasma.

Calculation of plasma volume shifts

Plasma volume shifts (changes in plasma volume due to exercise) were calculated according to the equation by Dill and Costill [9]. Complete blood counts were performed at each study time point using a COULTER® Ac•T diff ™ Hematology Analyzer (Beckman Coulter, Inc., Brea, California, USA), which yielded the hematocrit and hemoglobin values that were used in these calculations. Plasma volume shifts were determined in order to indicate the effect that exercise may have on fluid shifts, which may affect concentrations of the adrenal hormones and the metabolic biomarkers.

Statistical analysis

Statistical analyses were performed using SAS version 9.3 and significance was set *a priori* at p 0.05. Wilcoxon rank sum tests were used to compare study variables between groups, while Wilcoxon signed rank tests were used to compare study variables within groups. Although nonparametric statistics were used for analysis, data are presented as mean ± standard deviation (SD) to allow for easier comparison between the results of the current study and results from other published studies.

Results

Subjects

There were 9 subjects in the breast cancer survivor group and 9 subjects in the control group. Subject physical characteristics are presented in Table 1. The control group was significantly older than the breast cancer survivor group (p = 0.013); however, there were no other statistically significant physical differences between the groups. Most importantly, the groups were nearly identical in cardiovascular fitness (i.e., VO_{2peak}) and achieved nearly identical peak workloads during the VO_{2peak} test.

Treatment details for the breast cancer survivor group are presented in Table 2. Treatments were for a first-time diagnosis of breast cancer (i. e., subjects were not being treated for breast cancer recurrence or relapse). The 6 subjects who reported use of Tamoxifen and Letrozole had been using these medications anywhere from 3 weeks to 18 months prior to enrollment. Other medications used by the breast cancer survivor group that did not relate to cancer and its treatments included the following: esomeprazole (1 subject), vitamin/mineral/ nutritional supplements (3 subjects), anti-depressants/anti-anxiety medications (3 subjects), beta-blocker (1 subject), statins (1 subject), levothyroxine (1 subject), zolpidem (2 subjects), valadicyclovir (1 subject), and warfarin (1 subject). Similarly, medications used by the control group included the following: amitzia (1 subject), vitamin/mineral/nutritional supplements (3 subjects), anti-depressant/anti-anxiety medications (2 subjects), raloxifene (1 subject), anti-hypertensive medications (2 subjects), low-dose aspirin (2 subjects), statins (1 subject), loratadine (1 subject), and levothyroxine (1 subject).

Submaximal heart rate, VO$_2$ responses, rpe, pss scores, and plasma volume shifts

Heart rate, RPE, workload, and VO$_2$ responses to the submaximal exercise session as well as PSS scores for laboratory visits 2 and 3 are presented in Table 3. Submaximal VO$_2$ during the 30-min exercise session was similar between breast cancer survivors and controls, as were submaximal workload, pre-exercise resting heart rate, exercise heart rate, and RPE. Additionally, both groups reported similar PSS scores for visits 2 and 3. Exercise and recovery patterns of plasma volume shifts ranged from -2.8 ± 6.3 % to -11.8 ± 3.8 % in the breast cancer survivor group and -0.1 ± 9.2 % to -11.5 ± 4.6 % in the control group and did not differ significantly ($p = 0.87\text{-}1.00$).

Epinephrine, norepinephrine, and cortisol responses

All absolute plasma hormone concentrations are reported in Table 4. Blood samples could not be obtained from one breast cancer survivor subject immediately post-exercise and one breast cancer survivor subject 2 h post-exercise. All concentrations were found to be within acceptable ranges for the respective hormone as reported by the ELISA assay manufacturers. Pre-exercise plasma epinephrine levels were significantly higher in the breast cancer survivor group compared to the control group ($p = 0.005$). Immediately post-exercise, epinephrine levels were still somewhat elevated in the breast cancer survivor group compared to the control group ($p = 0.066$). When examining changes across time (i. e., comparing post-exercise epinephrine levels with pre-exercise plasma epinephrine levels), epinephrine levels did not change significantly in the breast cancer survivor group from pre-exercise to either of the 2 post-exercise time points ($p = 0.148\text{--}0.461$). In the control group however, epinephrine levels were significantly elevated immediately post-exercise compared to pre-exercise levels ($p = 0.031$) and continued to be somewhat elevated at 2 h post-exercise ($p = 0.063$).

Plasma norepinephrine levels were similar between the breast cancer survivor group and the control group pre-exercise and at both post-exercise time points ($p = 0.481\text{--}0.671$). Compared to pre-exercise levels, norepinephrine levels were somewhat elevated immediately post-exercise ($p = 0.055$). At 2 h post-exercise, norepinephrine levels were significantly elevated in both the breast cancer group ($p = 0.008$) and the control group ($p = 0.020$). In the

breast cancer survivor group, cortisol levels did not change significantly from pre-exercise to immediately post-exercise or from pre-exercise to 2 h post-exercise (p > 0.742). In the control group, cortisol levels were significantly lower immediately post-exercise and 2 h post-exercise compared to pre-exercise levels (p = 0.039 and 0.027 respectively). However, cortisol levels were not significantly different between the breast cancer survivors and the controls pre-exercise and at both post-exercise time points (p > 0.132).

Respiratory exchange ratio, free fatty acid, glucose, and lactate responses

Respiratory exchange ratio (RER), plasma FFA, glucose, and lactate responses are also presented in Table 4. Respiratory exchange ratio data were averaged for each subject from the expired gas data that was collected during the first, third, seventh, and tenth exercise interval. The breast cancer survivors displayed a significantly higher RER value over the course of the 30-min exercise session compared to the control group (p = 0.033), indicating that the breast cancer survivors were utilizing more carbohydrate for fuel during exercise, whereas the controls were utilizing an approximately equal amount of carbohydrate and lipid. Free fatty acid levels were similar between the breast cancer survivor group and the control group pre-exercise and immediately post-exercise, (p > 0.425). In both groups, FFA levels were significantly elevated immediately post-exercise compared to pre-exercise levels (p = 0.008). However, at 2 h post-exercise, the breast cancer survivor group exhibited significantly higher FFA levels compared to the control group (p = 0.024), whereas the control group returned to near pre-exercise levels. Plasma glucose levels were similar between the breast cancer survivor group and the control group pre-exercise and at both post-exercise time points (p > 0.132). Glucose levels significantly decreased immediately post-exercise compared to pre-exercise levels in the breast cancer survivor group (p = 0.016) while decreasing somewhat in the control group (p = 0.074). At 2 h post-exercise, glucose levels had returned to near pre-exercise levels in both groups (p = 0.129–0.844). Plasma lactate levels rose significantly in both groups immediately post-exercise compared to pre-exercise levels and continued to be significantly elevated in both groups at 2 h post-exercise (p < 0.016). Lactate levels were also largely similar between groups across time (p > 0.09).

Discussion

This was an exploratory investigation aimed to examine and compare catecholamine and cortisol responses along with metabolic biomarker responses to an acute bout of moderate-intensity intermittent exercise in recent breast cancer survivors and matched healthy controls. Although the study sample was small, this data does provide new and insightful results. It is important to note that the "physical stress" of the 30 min of submaximal exercise performed by both groups was highly comparable; that is, the oxygen requirements (VO_2), workload, heart rate response and RPE perception of exercise effort were nearly identical between the 2 groups. This is critical, as the responsiveness of stress hormones is directly proportional to the physical demands placed on the body [30]. However, it is important to note that the intermittent nature of the exercise training protocol may have stimulated the metabolic and hormonal responses differently than continuous exercise. Nevertheless, the precise control of exercise intensity using indirect calorimetry to ensure that all subjects performed at the exact same level of intensity, as well as the non-significant

differences in workload levels, HR, and RPE between groups, allows for better interpretation of study results.

Changes in plasma catecholamine, cortisol, and metabolic biomarker responses

The findings of this study regarding the catecholamine responses to the acute aerobic exercise session are novel. First, it was observed that the breast cancer survivor group showed little change in epinephrine levels, whereas the control group displayed what is considered to be a typical response [30]. At the same time, both groups exhibited similar norepinephrine responses to the acute exercise session that would be considered typical for such exercise [30, 31].

Epinephrine is critical in promoting glycogenolysis during exercise, allowing glucose to be released so that skeletal muscles can produce energy through glycolysis [30, 31]. The results of this study demonstrated that lactate, a major byproduct of glycolysis, was significantly elevated in both groups immediately post-exercise and 2 h post-exercise compared to pre-exercise levels. At the same time, plasma glucose levels were significantly reduced immediately post-exercise in the breast cancer survivor group and somewhat in the control group. The blunted epinephrine response in the breast cancer survivor group may imply that these individuals were not significantly relying on the action of epinephrine to provide glucose to the muscles during the exercise bout. Without a typical epinephrine response, the breast cancer survivors may have been relying more heavily on circulating glucose rather than the glucose that would have been available through muscle glycogen stores. This may explain the more notable decrease in blood glucose observed in the breast cancer survivors immediately post-exercise compared to the controls. In contrast, the control group would have been able to utilize a greater amount of glucose coming directly from muscle glycogen stores, thereby sparing the use of circulating glucose that would have come from hepatic glycogen stores. However, these notions are speculative for this current study.

Epinephrine and norepinephrine are also implicated in the hormonal regulation of lipid metabolism. Epinephrine activates hormone-sensitive lipase in adipose tissue, thus promoting lipolysis and the release of glycerol and FFA into circulation [29–31]. Sympathetic neurons (which release norepinephrine) innervate adipose tissue and, when activated, also promote lipolysis and the subsequent release of glycerol and FFA [29]. Both groups experienced a significant increase in FFA levels immediately post-exercise, which likely reflects the increases that were seen in one or both catecholamines at this time point. However, FFA levels continued to increase in the breast cancer survivor group 2 h post-exercise, whereas FFA levels in the control group were beginning to return to pre-exercise levels. This may be related to the fact that at 2 h post-exercise, norepinephrine levels were elevated above immediate post-exercise levels in the breast cancer survivor group but not in the control group, which may indicate that lipolysis and the rate of FFA release was still increasing in the breast cancer survivors but not in the controls.

Interestingly, the absolute plasma epinephrine concentrations were consistently higher in the breast cancer survivor group compared to the control group, particularly pre-exercise. Since the majority of epinephrine originates in the adrenal gland, this finding implies that the breast cancer survivors may have been experiencing a higher degree of chronic adrenal stress

reactivity. Previous research has shown that plasma epinephrine levels can be chronically elevated in breast cancer patients, possibly as a result of psychological distress related to the cancer and its treatments, which may have had more of an effect on the signaling pathways that activate the adrenal medulla vs. the adrenal cortex (hence why a similar effect was not observed with cortisol) [1, 20]. The current study did not ask the breast cancer survivors to report treatment-related side effects or distress levels, but such associations certainly warrant further investigation. Since the majority of norepinephrine is released from sympathetic neurons, the finding that the exercise bout elicited similar norepinephrine responses in both groups suggests that sympathetic nervous system stimulation was not significantly different in the breast cancer survivors compared to the controls. This notion is further supported by the fact that both groups exercised at the same relative intensity and displayed nearly identical cardiovascular responses (Table 3), which norepinephrine is critical in regulating [30, 39].

The findings of this study regarding the cortisol responses to the acute aerobic exercise session are also novel. Cortisol levels showed little change across time in the breast cancer survivor group but showed significant decreases immediately post-exercise and 2 h post-exercise in the control group. Exercise-induced fluctuations in plasma cortisol levels typically follow a threshold effect in which exercise intensities of 60 % of VO_{2max} characteristically elicit increased plasma cortisol concentrations, and intensities below this threshold typically cause significant decreases in blood cortisol levels [30]. Thus, the cortisol exercise responses in the current study appear atypical, but the discontinuous nature of the aerobic exercise session may not have elicited the same amount of physiological stress as would a continuous aerobic exercise session of the same intensity and duration. Furthermore, the intensity prescription for the current study was based on VO_{2peak} and not VO_{2max} (VO_{2peak} intensities are usually slightly lower than VO_{2max}). Thus, the exercise may not have reached the threshold that was necessary for eliciting an increase in plasma cortisol concentration, and the decreases in plasma cortisol may have occurred because the rate of removal exceeded the rate of secretion [30]. Cortisol is instrumental in promoting lipolysis and subsequent release of FFA into the blood. However, since cortisol levels did not increase in either group in response to the exercise session, it is likely that the rise in FFA that occurred with exercise is more related to the changes in epinephrine and norepinephrine as previously discussed.

Previous research has also shown that breast cancer survivors may experience significant alterations in their cortisol secretion patterns, including disruptions in the circadian rhythm of the HPA axis as well as disturbances in normal HPA axis feedback inhibition [36, 37, 41]. Such alterations in the normal function of the HPA axis are likely a result of breast cancer treatments experienced by these individuals [4, 14, 34]. For example, selective estrogen receptor modifiers (SERMs) such as Tamoxifen may have a suppressive effect on adrenal corticosteroid release, possibly due to a downregulation in the sensitivity of the adrenal glands to adrenocorticotropic hormone (ACTH) [18]. All 9 of the breast cancer survivors in this study received chemotherapy and 6 were receiving hormonal therapy medications including tamoxifen and letrozole, thus supporting this notion.

Comparisons with previous research

Previous work by Evans et al. and Tosti et al. examined metabolic biomarker responses to 9-min bouts of continuous acute aerobic exercise at 40 %, 60 %, and 70 % of estimated VO_{2max} in breast cancer survivors and healthy controls [11, 40]. Evans et al. observed that breast cancer survivors exhibited significantly lower blood lactate levels in response to the exercise bout at 70 % of estimated VO_{2max}, whereas Tosti et al. observed that post-exercise blood lactate levels in the breast cancer survivors were significantly lower lactate levels across all 3 exercise intensities [11, 40]. Moreover, Tosti et al. reported that the breast cancer survivor group experienced significantly higher lipid oxidation and lower carbohydrate oxidation rates across all 3 exercise intensities, and that breast cancer survivors displayed less of a decrease in blood glucose levels post-exercise compared to controls [40]. The results of these 2 studies suggested that breast cancer survivors may have experienced altered substrate utilization during exercise compared to physically similar women who have never experienced cancer treatment; i. e., the breast cancer survivors were using less glucose and more FFA in order to fuel exercise of the same relative intensity compared to the healthy controls. Tosti et al. speculated that the reduced oxidation of carbohydrates in the breast cancer survivor group during exercise may have been the result of one or more factors, including reduced availability of glucose to the skeletal muscle, reduced uptake of glucose by the skeletal muscle, or a compromise in glycolysis itself or the factors controlling glycolysis within the muscle [40]. Research from other laboratories has indicated that breast cancer therapies are associated with the development of insulin resistance, thus creating a compromised ability to uptake blood glucose and/or the biochemical pathways for its usage [28]. In light of this potentially compromised glucose metabolism, the muscle cell would need to utilize alternative fuel sources, specifically lipid.

The results of the present study are somewhat different from the previous results of Evans et al. and Tosti et al. [11, 40]. The present study showed that while immediate post-exercise lactate levels were lower in the breast cancer survivor group compared to the control group, they were only somewhat lower (p = 0.094). Additionally, the breast cancer survivor group in the present study actually displayed lower plasma glucose levels and higher plasma FFA levels compared to the control group immediately post-exercise, thus implying that breast cancer survivors were utilizing more glucose and less FFA during the exercise session. This is further supported by the difference in respiratory exchange ratio (RER) that was observed in this study, where the breast cancer survivor group had an average RER of 0.91 and the control group had an average RER of 0.84 over the course of the 30-min exercise session. Respiratory exchange ratios typically range from 0.7–1, where RER values closer to 0.7 indicate a greater utilization of lipids, values close to 0.85 indicate approximately equal utilization of lipids and carbohydrates, and RER values closer to 1 indicate a greater utilization of carbohydrates. Thus, the breast cancer survivor group appeared to be utilizing more carbohydrates and less FFA compared to the control group specifically during the 30-min exercise session, although this was not clearly reflected in the blood lactate levels immediately post-exercise. It should be noted that the exercise sessions that were used in the studies by Evans et al. and Tosti et al. were continuous aerobic exercise sessions of only 9 min in duration, whereas the current study used a discontinuous aerobic exercise session of 30 min in duration, which may primarily explain the differing results seen among these

studies. It should also be noted that for the current study, RER data was only obtained for the duration of the 30-min exercise session and not during the 2-h recovery period, in which a significant difference in FFA levels was observed between groups. As mentioned previously, this rise in FFA levels at 2 h post-exercise in the breast cancer survivor group may have been related to concomitant rise in norepinephrine levels that also occurred at 2 h post-exercise in this group.

Strengths and limitations

This study is one of the first to describe endocrine responses to acute aerobic exercise in breast cancer survivors and only one of a few to describe changes in substrate mobilization and utilization during acute aerobic exercise. As with any study, there are limitations to the present investigation. First, the average age differed between the study groups. While all attempts were made to match subjects closely on all physical and fitness characteristics, the control group was older than the breast cancer survivor group by an average of 9 years. However, this was the only physical characteristic difference between the groups. Second, the study employed a relatively small sample size. Third, this study employed a discontinuous exercise protocol, the results of which may or may not have been the same had a continuous exercise protocol been utilized. Additionally, this study may have obtained different results if study participants were more aerobically fit because endurance training improves metabolic efficiency, reduces reliance on glucose, and enhances reliance on FFA for energy production during acute aerobic exercise. Furthermore, other endocrine controls of metabolism such as glucagon, insulin, and growth hormone, were not measured, which may have given additional insight into the changes that were observed in FFA, glucose, and lactate. Finally, some data points were not available for all subjects because of limited availability of blood samples, or the inability to obtain blood samples, a common occurrence in patient populations. These missing specimens accounted for less than 5 % of the total blood specimens obtained, and accepted statistical procedures allowed for appropriate analysis.

Given these limitations, the results of this study do provide meaningful information about the exercise responses of individuals who have low cardiorespiratory fitness levels due to being sedentary and/or as a result of cancer treatments. When particularly considering oncology patients, the side effects of chemotherapy and other cancer treatments often leave these individuals with compromised cardiopulmonary functioning and hence a lower level of physical functionality. Therefore, it is crucial to investigate how exercise impacts physiological responses in these less fit individuals. The information gained from this and other studies aims to shed light on the effect of exercise on the multiple aspects of physical functioning in the oncology patient population, particularly for those individuals who are in the beginning stages of a structured exercise program and must exercise at lower intensities, for shorter durations, and/or in an interval-like fashion.

Conclusion

In summary, 30 min of moderate-intensity intermittent aerobic exercise seemed to elicit attenuated epinephrine and cortisol responses in breast cancer survivors compared to

physically similar control women without a history of cancer diagnosis or treatment. Norepinephrine responses appeared to be similar in both groups. These hormonal responses to the exercise session were reflected in the decreased plasma glucose, increased plasma FFA, and increased RER that were especially seen in the breast cancer group. The present study did not address the exact reasons behind the altered adrenal gland function in the breast cancer survivors or the effects of other hormonal controls on metabolism such as glucagon, insulin, or growth hormone. Additional research investigating the effect of acute aerobic exercise on the neuro-endocrine system and metabolic pathways in cancer patients and survivors is warranted. Furthermore, future studies examining the effects of aerobic exercise training on acute metabolic and hormonal responses to exercise in cancer patients will aid in providing greater insight into how these individuals respond to and recover from aerobic exercise. Whereas some endocrine and metabolic responses were different between the controls and the breast cancer survivors in this study, both groups successfully completed the exercise session and other markers of exertion (i. e., HR and RPE) were similar between groups. Therefore, this work is supportive of moderate-intensity aerobic exercise performed in intervals of short bouts as being well tolerated in recently treated breast cancer survivors, as it is for similar individuals without a history of cancer who are physically very deconditioned.

Acknowledgments

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Table 1

Subject physical characteristics, VO_{2peak}, and peak workload (mean ± SD).

Characteristic	Breast Cancer Survivor Group (n = 9)	Control Group (n = 9)	p-value
Age (years)	50 ± 6	59 ± 5	0.013
Race (# of women)	Caucasian (8) African American (1)	Caucasian (9)	–
Height (cm)	164.7 ± 5.8	163.8 ± 5.9	0.931
Weight (kg)	76.9 ± 12.6	77.7 ± 13.3	0.931
Body mass index (kg/m^2)	28.4 ± 5.0	29.0 ± 4.6	0.862
Percent body fat (%)	41.6 ± 4.5	42.1 ± 4.0	0.761
VO_{2peak} (mL/kg/min)	18.1 ± 2.7	18.5 ± 5.1	0.862
Peak workload (W)	107 ± 19	106 ± 17	0.925

Table 2

Details of cancer treatments received by breast cancer survivor group (n = 9).

Treatment	Number of Subjects Receiving Treatment
Surgery	
Mastectomy	4
Lumpectomy	5
Radiation therapy	9
Chemotherapy	
Doxorubicin	6
Cyclophosphamide	7
Paclitaxel/Docetaxel	9
Carboplatin	3
Hormonal therapy	
Tamoxifen	5
Letrozole	1
Other	
Trastuzumab	2
Lapatinib	1
Bevacizumab	1

Table 3

Submaximal heart rate, rating of perceived exertion, workload, VO_2 responses, and Perceived Stress Scale scores (mean ± SD).

Parameter	Breast Cancer Survivor Group	Control Group	p-value
Submaximal VO_2 (mL/kg/min)	12.1 ± 1.3	11.1 ± 2.1	0.284
Submaximal workload (W)	59 ± 9	62 ± 11	0.728
Resting HR (bpm)	68 ± 6	66 ± 9	0.662
Exercise HR (bpm)	122 ± 18	119 ± 16	0.602
RPE	12 ± 1	12 ± 1	0.728
PSS score for laboratory visit 2	15 ± 4	13 ± 6	0.436
PSS score for laboratory visit 3	15 ± 5	12 ± 7	0.232

Table 4

Respiratory exchange ratio and plasma hormone and metabolic biomarker levels across time (mean ± SD).

Parameter	Breast Cancer Survivor Group	Control Group
Epinephrine (pg/mL)		
Pre-exercise[a]	49.7 ± 9.9	27.1 ± 5.7
0 h post-exercise	55.4 ± 13.9	39.7 ± 14.8 *
2 h post-exercise	43.0 ± 3.3	36.1 ± 16.8
Norepinephrine (pg/mL)		
Pre-exercise	258.0 ± 109.6	518.0 ± 555.3
0 h post-exercise	515.5 ± 433.5 *	745.2 ± 729.4 *
2 h post-exercise	527.3 ± 381.3[†]	715.2 ± 488.8[†]
Cortisol (ng/mL)		
Pre-exercise	137.7 ± 73.2	147.7 ± 49.2
0 h post-exercise	133.2 ± 85.0	76.5 ± 17.0 *
2 h post-exercise	93.8 ± 69.1	85.8 ± 31.1[†]
Free fatty acid (mEq/L)		
Pre-exercise	0.28 ± 0.09	0.27 ± 0.05
0 h post-exercise	0.57 ± 0.19 *	0.49 ± 0.14 *
2 h post-exercise[b]	0.63 ± 0.18[†]	0.37 ± 0.20
Glucose (mg/dL)		
Pre-exercise	92.8 ± 7.7	97.9 ± 8.7
0 h post-exercise	84.3 ± 10.5 *	93.6 ± 7.8
2 h post-exercise	94.0 ± 23.7	86.0 ± 17.0
Lactate (mmol/L)		
Pre-exercise	0.89 ± 0.14	0.91 ± 0.15
0 h post-exercise	4.33 ± 2.12 *	5.93 ± 1.57 *
2 h post-exercise	1.74 ± 0.35[†]	1.93 ± 0.37[†]
Respiratory exchange ratio (RER)[c]	0.91 ± 0.05	0.84 ± 0.04

[a] $p < 0.05$ for comparing pre-exercise values between groups

[b] $p < 0.05$ for comparing 2 h post-exercise values between groups

[c] $p < 0.05$ for comparing RER values between groups

* $p < 0.05$ for pre-exercise vs. 0 h post-exercise

[†] $p < 0.05$ for pre-exercise vs. 2 h post-exercise