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Aerobic physical activity and salivary cortisol levels among women with a history of breast cancer

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ABSTRACT

Background: Physical activity (PA) helps reduce cancer-related symptoms and improves overall functioning for women with and without a history of breast cancer (BC). Few researchers have examined the associations between PA and physiological stress measures. The aim of this study was to determine whether aerobic PA was associated with diurnal and reactive cortisol patterns, and whether these associations differed for women with and without a history of BC.

Methods: Participants were 25 women with a history of BC and 23 women without a history of BC who self-reported aerobic PA frequency. To assess diurnal cortisol patterns, participants provided five saliva samples collected on two consecutive days at the following times: upon awakening, 30 min after waking, 12 PM, 4 PM, and 9 PM. To measure reactive cortisol patterns, participants provided seven saliva samples collected before, during, and after doing the Trier Social Stress Test.

Results: Cortisol patterns differed statistically based on women's cancer history, whereby women without a history of BC had significantly higher overall cortisol reactivity to an acute stressor, and a marginally significant (p = .05) cancer experience by aerobic PA interaction was observed when analyzing diurnal cortisol data.

Conclusions: Findings suggest that PA may not have the same effect on women with and without a history of BC.

1. Introduction

In recent decades, there has been a surge in the number of studies focusing on identifying the benefits of physical activity (PA) for women diagnosed with breast cancer (BC).[1–3] There is now robust evidence showing that PA can decrease cancer-related fatigue, improve overall physical functioning, and reduce the risk of cancer recurrence in this population.[4–11] There is also evidence showing that PA can improve mood and reduce stress, anxiety, and depression in women diagnosed with BC.[12–15] In light of this body of literature, PA is now recognized as being safe and beneficial for women with a history of BC, and thus should be widely promoted.[1,16–19] Notwithstanding the evidence that PA confers numerous health benefits for women diagnosed with BC, much of the evidence linking PA to psychological health benefits is based on data collected via questionnaires assessing psychological health outcomes. As a result, whereas the positive effect of PA on self-reported mood and stress are well established,[13,20,21] the effects of PA on physiological measures of stress are still unclear. Some investigators have started to explore the association between PA and biomarkers in people diagnosed with cancer.[22] Cortisol is one biomarker that plays an essential role in energy metabolism, information processing, and stress responsiveness. It is commonly used to assess the activity of the hypothalamic-pituitary-adrenal (HPA) axis, a system that tightly regulates the stress response.[23,24] In the single study that examined the effect of PA on cortisol secretion among women receiving treatment for BC (n = 20), no significant relationship between PA and cortisol was found other than a trend toward lower cortisol levels in the PA intervention group.[25] However, it is not possible to render a conclusion about the relationship between PA and cortisol in women who have completed treatment for BC based on this study.

The importance of studying whether PA can have a normalizing effect on the cortisol secretion patterns among women once treatment for BC has ended is highlighted by findings showing that these women typically exhibit a flatter cortisol pattern in response to an acute stressor compared to women with no history of cancer.[26–28] An abnormal cortisol concentration pattern in response to acute stress situations can lead to various negative health consequences because cortisol is essential for regulating bodily functions and responding to environmental challenges.[23] Indeed, persistent low cortisol levels have been linked to pain, fatigue, high-stress sensitivity,[29] and increased

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vulnerability to stress-related bodily disorders.[30,31] Moreover, mortality, disease severity, and several other negative health outcomes such as obesity,[32] depression,[33] and diabetes[34] have been associated with general dysregulation of the HPA axis (i.e., atypical cortisol concentration patterns).[35,36]

As several studies have reported that abnormalities in the cortisol secretion patterns of women treated for BC[26–28,35,37–39] and given evidence of the benefits of PA on the overall health-related outcomes for women diagnosed with BC,[1,3] it is important to investigate whether PA plays a protective role in the cortisol dysregulation found in women with a history of BC. In doing so, it is valuable to compare whether the role is comparable to that of women without a history of BC. Previous studies with adults without a history of cancer and with athletes both indicate that PA influences the functioning of the HPA axis and regulates cortisol secretion,[40,41] whereby PA generates an almost immediate HPA response by activating and stimulating cortisol releases. The long-term effect of PA on cortisol patterns, however, remains uninvestigated in these populations (as well as in women with a history of BC). The purpose of the present study was to extend this research and evaluate the association between aerobic PA and cortisol patterns among women with a history of BC who were, on average, 6.5 years post-adjuvant treatment as well as with women without a history of BC. The specific objectives were twofold: (1) assess whether aerobic PA was associated with diurnal and reactive cortisol patterns, and (2) determine whether the association between aerobic PA and cortisol patterns differed between women with and without a history of BC. It was hypothesized that women with a history of BC who reported engaging in aerobic PA more frequently at the time of testing (moderate/high-PA group) would exhibit significantly less abnormalities in their cortisol patterns than those who reported engaging in aerobic PA less frequently or not at all (no/low-PA group). Given the exploratory nature of the second aim, no hypothesis regarding whether a cancer experience moderated the association between aerobic PA and cortisol patterns was proposed.

2. Methods

2.1. Participants

Women with and without a history of BC were recruited through printed advertisements and cancer support groups. To be eligible for this study, women with a history of BC had to meet the following criteria: (a) have been diagnosed with stage 0-III BC, (b) be more than 6 months post-adjuvant treatment (i.e., surgery, chemotherapy, and/or radiation therapy) for BC, and (c) be able to read and speak English. Women without a history of BC had to meet the following criteria: (a) have completed a routine mammography screening with negative results, (b) have no history of other types of cancer (except non-invasive skin cancer and cervical cancer), and (c) be able to read and speak English. Women were not eligible if they: (a) had a substance abuse problem, (b) were suffering from a major disabling conditions interfering with their quality of life and level of functioning (e.g., psychiatric disorders), and/or (c) were breastfeeding, pregnant, or taking any medication that could alter hormonal secretion (e.g., hydrocortisone, hypnotics, benzodiazepines).

2.2. Procedures

The study protocol was approved by the University of Ottawa's Research Ethics Review Board. All participants provided written informed consent prior to data collection, received financial compensation for travel ($50 CAD), and were entered in a raffle to win one of four $250 CAD gift certificates. Once eligibility was confirmed over the phone, women were scheduled to attend two laboratory visits at the University of Ottawa Stress, Immunocompetence, and Health Laboratory. The first visit lasted approximately 30 min and served to obtain informed consent, provide instructions on the collection of saliva samples, and supply participants with labeled salivettes. Participants were asked to collect five saliva samples on two consecutive days at the following times: at awakening, 30 min after waking, 12 PM, 4 PM, and 9 PM. Commensurate with recommended protocols,[42] participants were instructed to rinse their mouth 10 min before saliva collection in order to avoid sample dilution, to place the salivette directly under their tongue for 3 min, and to store the salivettes in the refrigerator until delivery to the laboratory for the second visit (approximately 1 week after their first visit). Further, participants were asked to refrain from smoking and drinking alcohol 24 h prior to saliva collection, as well as avoid caffeine products and exercising 1 h before saliva collection. Upon arrival at the Laboratory, the saliva samples were transferred to Eppendorf tubes and stored in a freezer at −80 °C until processed for cortisol.

The second visit lasted approximately 2 h and served to assess participants' reactive cortisol responses. During this visit, participants were subjected to the Trier Social Stress Test (TSST; see description below)[43] at which time seven saliva samples were collected. The first sample was collected upon arrival at the laboratory ("arrival" sample), the second and third during the TSST (i.e., "anticipation" sample which occurred between the speech preparation and the speech delivery; "arithmetic" sample which occurred upon completion of the arithmetic task). After completing the TSST, participants were taken to a quiet room for 1 h to complete a questionnaire assessing sociodemographic characteristics and aerobic PA. Four additional saliva samples were collected during this time: 10, 20, 40, and 60 min after the TSST. Second visits were conducted between 3 PM and 5 PM in order to coincide with the time at which cortisol levels are near their lowest and most stable daytime values.[44]

2.3. Measures

2.3.1. Cortisol levels

Cortisol was assessed using commercially available highly-sensitive enzyme-linked immunosorbent assay (ELISA). The assay kits and the protocols was provided by Salimetrics, State College, PA, USA.[42] For diurnal cortisol, cortisol concentrations were assessed on two consecutive days and the means of each of the five time points were subsequently computed for each participant. For reactive cortisol, cortisol concentrations were assessed before, during, and after the TSST as described previously. The TSST is a two-task protocol that has been designed to induce a physiological stress response.[45,46] A detailed overview of the TSST protocol has previously been published.[43] Briefly, the task consists of a 5-min mock interview and a 5-min arithmetic subtraction task in front of three confederate evaluator judges. Participants were told that the session would be video-taped for later review. The TSST has successfully been shown to induce subjective stress, cardiovascular changes, and endocrine responses.[45,46]

2.3.2. Aerobic PA

A single item was used to assess participants' engagement in aerobic PA. Participants reported how often they participated in cardiovascular activities per week. Cardiovascular activity was described to participants as any exercise, regardless of its intensity, that raises heart rate. Response options were: *once per week or less*, *2–3 times per week*, *4–5 times per week*, and *6–7 times per week*, and *more than 7 times per week*. Responses were then dichotomized into 'no/low PA' and 'moderate/high PA' levels based upon two different methods. For the first dichotomization (PA1), participants who reported engaging in aerobic PA once per week or less were placed in the 'no/low PA' group and all other participants in the 'moderate/high PA' group. For the second dichotomization (PA2), participants who reported engaging in aerobic PA three times per week or less were placed in the 'no/low PA' group and other participants in the 'moderate/high PA' group. We divided PA frequency both ways to determine if the groups would be distinguished by difference in PA frequency, i.e., none or almost none vs. irregular PA (PA1) and none, almost none, or irregular vs. regular PA (PA2). The sample sizes were insufficient to analyze the data based on a tertiary scheme reflecting low, moderate, and high PA frequencies.

2.4. Data preparation and analyses

2.4.1. Data preparation

Once collected from participants, the saliva samples were transferred to Eppendorf tubes and stored in a −80 °C freezer; they were processed in duplicate within 3 months at the University of Ottawa Stress, Immunocompetence, and Health Laboratory using commercially available highly-sensitive enzyme linked immunosorbent assay kits and the protocol designed by Salimetrics, State College, PA, USA. For diurnal cortisol, the means and standard deviations were computed for samples taken at the same time across both days, yielding five scores in mol/L per participant, which were then used to determine the area under the curve to increase (AUCi) using trapezoidal integration methods[47] to represent participants' overall daily cortisol secretion level. For reactive cortisol, the seven saliva samples collected during the TSST protocol were used to compute the AUCi representing participants' individual overall cortisol response to stress.

Data were screened for missing responses, which amounted to less than 5% overall and were typically due to insufficient saliva amounts. The expectation-maximization (EM) algorithm was used to impute missing values when participants had no more than two missing data points (out of 10) for diurnal cortisol and no more than three (out of seven) for reactive cortisol; otherwise data of those participants missing more values were excluded from the current analyses. Based on these criteria, the data associated with seven participants were eliminated, leaving a total of 48 participants. Data were also screened for outliers and tested for assumptions of homogeneity of variance, sphericity, and normality.[48]

2.4.2. Statistical analysis

Data analyses were performed using SPSS version 21.0.[49] Two-way analysis of variance (ANOVA) and mixed-design ANOVA were used to evaluate diurnal and reactive cortisol patterns. Two-way ANOVAs were first computed to examine between-group differences in cortisol patterns based on cancer experience (no history vs. history of BC) and aerobic PA (no/low vs. moderate/high PA group); the total cortisol AUCi score served as the dependent variable. Second, three-way mixed-design ANOVAs were performed to gain more insight into the pattern of diurnal and reactive cortisol concentrations. The between-subjects or randomized group factors were cancer experience (history vs. no history of BC) and aerobic PA (no/low vs. moderate/high PA group) and the within-subjects or repeated factor was time (*diurnal* – at awakening, 30 min after awakening, 12 PM, 4 PM, and 9 PM; *reactive* –arrival, anticipation, arithmetic, 10, 20, 40, and 60 min after the TSST). All analyses were conducted separately for the PA1 and PA2 dichotomization schemes. Factors such as age, socioeconomic status, and time since diagnosis were considered as potential covariates; however, none of them were significantly correlated with cortisol levels and were therefore not retained for analyses of covariance.

3. Results

3.1. Participants characteristics

The demographic characteristics of the 48 participants included in the current study are depicted in Table 1. The participants were, on average, 57.9 years of age at study inception. Most were married (56.3%), self-identified as White (91.7%), consumed less than one alcoholic beverage per day (91.6%), and did not smoke (95.8%). Also, 44% were retired and most (58.3%) had an annual family income below $80,000 CAD. There was no statistically significant group (cancer experience and PA frequency) difference on these demographic characteristics based on parametric (ANOVA) and non-parametric (chi-square) analyses. In the group consisting of women with a history of BC, the average age at diagnosis was 52.8 years (*SD* = 9.36; range = 32–76) and the average time since diagnosis was 6.5 years (*SD* = 3.34; range = 0.5–40). Most (64.0%) were diagnosed with stage 0 or I BC and underwent some combination of treatment, including lumpectomy (40.0%), chemotherapy (44.0%), radiation (60.0%), and hormone therapy (60.0%).

Table 1
Characteristics of participants.

Demographic characteristics	Participants: Women with a history of breast cancer (*N* = 25)	Women without a history of breast cancer (*N* = 23)
Age [mean years [SD] (Range)]	59.5 [10.1] (39.0-81.0)	56.3 [11.3] (29.0-73.0)
Ethnicity [*n* White (%)]	23 (92.0)	21 (91.3)
Relationship status [*n* (%)]		
Single	2 (8.0)	2 (8.7)
Common law	3 (12.0)	1 (4.3)
Married	14 (56.0)	13 (56.5)
Divorced/separated	4 (16.0)	5 (21.7)
Widowed	2 (8.0)	2 (8.7)
Highest level of education attained [*n* (%)]		
High school	6 (24.0)	7 (30.4)
College	5 (20.0)	3 (13.0)
Bachelor's degree	12 (48.0)	7 (30.4)
Graduate degree	2 (8.0)	6 (26.1)
Work status [*n* (%)]		
Blue collar	0	1 (4.3)
White collar	11 (44.0)	6 (26.1)
Self-employed	1 (4.0)	3 (13.0)
Medical leave of absence	3 (12.0)	1 (4.3)
Retired	9 (36.0)	12 (52.2)
Family income (CAD) [*n* (%)]		
< $40,000	4 (17.4)	4 (18.2)
$40,000 to $79,999	10 (43.5)	10 (45.5)
$80,000 to $119,999	6 (26.1)	4 (18.2)
≥ $120,000	3 (13.0)	4 (18.2)
Aerobic physical activity per week [*n* (%)]		
≤ 1 time	6 (24.0)	5 (21.7)
2 to 3 times	9 (36.0)	12 (52.2)
4 to 5 times	6 (24.0)	6 (26.1)
6 to 7 times	4 (16.0)	0
> 7 times	0	0

3.2. Diurnal cortisol

The analytical sample comprised of 19 women with a history of BC and 23 women without a history of BC. Fig. 1 provides plots of the data showing the relationship between aerobic PA frequency, cancer experience, and diurnal cortisol AUCi. Using the PA1 cutoff (Fig. 1, left), a two-way ANOVA yielded no significant main effect for cancer experience [$F(1,38) = 1.65$, $p = .206$, $\eta_p^2 = .04$] or aerobic PA [$F(1,38) = 2.11$, $p = .15$, $\eta_p^2 = .05$], nor a significant interaction between cancer experience and aerobic PA [$F(1, 38) = 1.40$, $p = .25$, $\eta_p^2 = .04$]. Using the PA2 cutoff (Fig. 1, right), a two-way ANOVA yielded no significant main effect for cancer experience [$F(1,38) = 0.02$, $p = .88$, $\eta_p^2 = .001$] or aerobic PA [$F(1,38) = 1.32$, $p = .26$, $\eta_p^2 = .03$], nor a significant interaction between cancer experience and aerobic PA [$F(1,38) = 0.99$, $p = .33$, $\eta_p^2 = .03$].

Fig. 2 displays the plots of the diurnal cortisol fluctuation pattern across five time points by cancer experience and aerobic PA frequency.

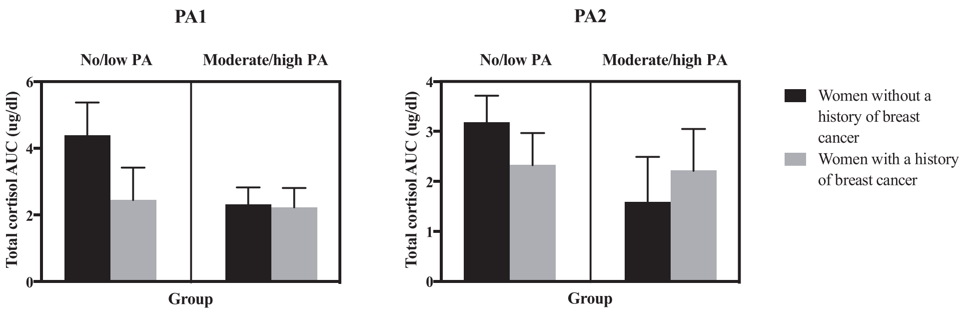

Fig. 1. Average diurnal cortisol AUCi scores for participants by cancer experience and aerobic PA frequency. On the left side (PA1), no/low PA plots participation in PA ≤ one time per week and moderate/high PA participation in PA ≥ two times per week. On the right side (PA2), no/low PA indicates participation in PA ≤ three times per week and moderate/high PA participation in PA ≥ four times per week.

Using the PA1 cutoff (Fig. 2, left), a mixed-design ANOVA yielded a significant main effect for time [F(1.99,75.71) = 33.74, p < .001, η_p^2 = .47], with the pattern suggesting typical diurnal cortisol fluctuation. No significant main effects were found for cancer experience [F(1,38) = 0.17, p = .68, η_p^2 = .004] or aerobic PA1 [F(1,38) = 0.47, p = .50, η_p^2 = .01]. In addition, no significant interactions were observed [cancer experience × time: F(1.99,75.71) = 0.93, p = .40, η_p^2 = .02; aerobic PA1 × time: F(1.99,75.71) = 0.54, p = .58, η_p^2 = .01; cancer experience × time × aerobic PA1: F(1.99,75.71) = 0.50, p = .61, η_p^2 = .01]; cancer experience × aerobic PA1: F(1,38) = 0.33 p = .57, η_p^2 = .01], indicating that the differences across time points were similar for participants with and without a history of BC who reported no/low and moderate/high PA.

Using the PA2 cutoff (Fig. 2, right), a mixed-design ANOVA yielded a significant main effect of time [F(2.03,77.02) = 42.22, p < .001, η_p^2 = .53] and no significant main effect for cancer experience [F(1,38) = 0.62, p = .44, η_p^2 = .02] or aerobic PA2 [F(1,38) = 1.53, p = .22, η_p^2 = .04]. A cancer experience × aerobic PA2 interaction effect was observed to approach significance [F(1,38) = 4.05, p = .05, η_p^2 = .10] due to group differences in the awakening and 30 min later response that was lower in women without a history of BC relative to those with a history of BC. No other significant interaction effects were observed [cancer experience × time: F(2.03,77.02) = 1.25, p = .29, η_p^2 = .03; aerobic PA2 × time: F(2.03,77.02) = 0.12, p = .89, η_p^2 = .003; cancer experience × time × aerobic PA2: F(2.03,77.02) = 2.39, p = .10, η_p^2 = .06].

3.3. Reactive cortisol

Fig. 3 provides plots of the data showing the relationship between aerobic PA frequency, cancer experience, and reactive cortisol AUCi. The analytical sample comprised 21 women with a history of BC and 22 women with no history of BC. Using the PA1 cutoff (Fig. 3, left), a two-way ANOVA yielded a significant main effect of cancer experience [F(1, 39) = 4.22, p = .05, η_p^2 = .10], whereby women without a history of BC had a significantly higher cortisol AUCi (M = 1.61, SD = 0.22) than women with a history of BC (M = 1.01, SD = 0.19), a non-significant main effect for aerobic PA1 [F(1,39) = 0.56, p = .50, η_p^2 = .01], and a non-significant interaction effect between cancer experience and aerobic PA1 [F(1,39) = 0.35, p = .56, η_p^2 = .01]. Using the PA2 cutoff (Fig. 3, right), a two-way ANOVA yielded no significant main effect of cancer experience [F(1,39) = 2.08, p = .16, η_p^2 = .05] or aerobic PA2 [F(1,39) = 0.05, p = .83, η_p^2 = .001], nor a significant interaction between cancer experience and aerobic PA2 [F(1,39) = 0.92, p = .34, η_p^2 = .02].

Fig. 4 displays the plots of the reactive cortisol pattern across seven time points during an acute stress situation by cancer experience and aerobic PA frequency. Using the PA1 cutoff (Fig. 4, left), a mixed-design ANOVA yielded a significant main effect for time [F(2.76,107.79) = 3.56, p = .02, η_p^2 = .08], supporting an expected difference in cortisol levels in response to an acute stressor. A significant main effect was found for cancer experience indicating that women without a history of BC had a significantly higher mean cortisol levels (M = 0.19, SD = 0.02) than women with a history of BC (M = 0.12, SD = 0.02). No significant main effect was found for aerobic PA1 [F(1,39) = .86, p = .36, η_p^2 = .02] and no significant interaction effects were observed [cancer experience × time: F(2.76,107.79) = 2.37, p = .08, η_p^2 = .06; aerobic PA1 × time: F(1.99, 107.79) = 0.79, p = .49, η_p^2 = .02; cancer experience × time × aerobic PA1: F(2.76, 107.79) = 0.97, p = .41, η_p^2 = .02]; cancer experience × aerobic PA1 [F(1,39) = .447, p = .51, η_p^2 = .01], indicating that the differences across time points were similar for participants with and without a history of BC who reported no/low and moderate/high PA.

Using the PA2 cutoff (Fig. 4, right), a mixed-design ANOVA yielded a significant effect for time [F(2.89,112.64) = 3.12, p = .03, η_p^2 = .07]. No significant main effects were found for cancer experience [F(1,39) = 2.65, p = .11, η_p^2 = .06] or aerobic PA2 [F(1,39) = 0.04, p = .84, η_p^2 = .001]. In addition, no significant interaction effects were observed [cancer experience × time: F(2.89,112.64) = 0.75, p = .52, η_p^2 = .02; aerobic PA2 × time: F(2.89, 112.64) = 0.26, p = .85, η_p^2 = .01; cancer experience × time × aerobic PA2: F(2.89, 112.64) = 1.66, p = .18, η_p^2 = .04]; cancer experience × aerobic PA2: F(1,39) = .71, p = .40, η_p^2 = .02], indicating that the differences across time points were similar for participants with and without a history of BC who reported no/low or moderate/high PA.

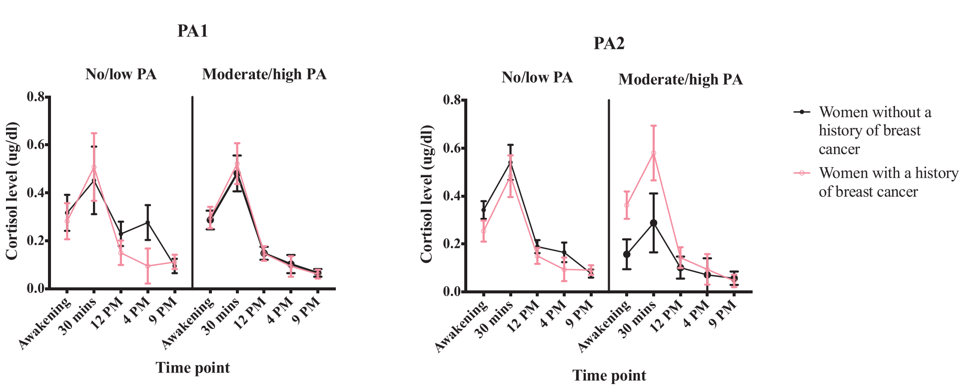

Fig. 2. Diurnal cortisol profiles of participants with and without a history of BC by aerobic PA frequency. On the left side (PA1), no/low PA plots participation in PA ≤ one time per week and moderate/high PA participation in PA ≥ two times per week. On the right side (PA2), no/low PA reflects participation in PA ≤ three times per week and moderate/high PA participation in PA ≥ four times per week.

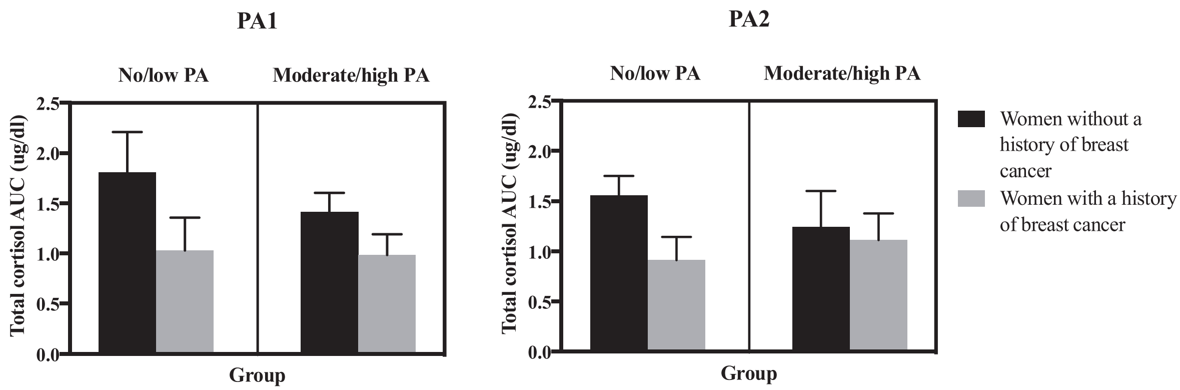

Fig. 3. Average reactive cortisol AUCi scores for participants by cancer experience and aerobic PA frequency. On the left side (PA1), no/low PA shows participation in PA ≤ one time per week and moderate/high PA participation in PA ≥ two times per week. On the right side (PA2), no/low PA shows participation in PA ≤ three times per week and moderate/high PA participation in PA ≥ four times per week.

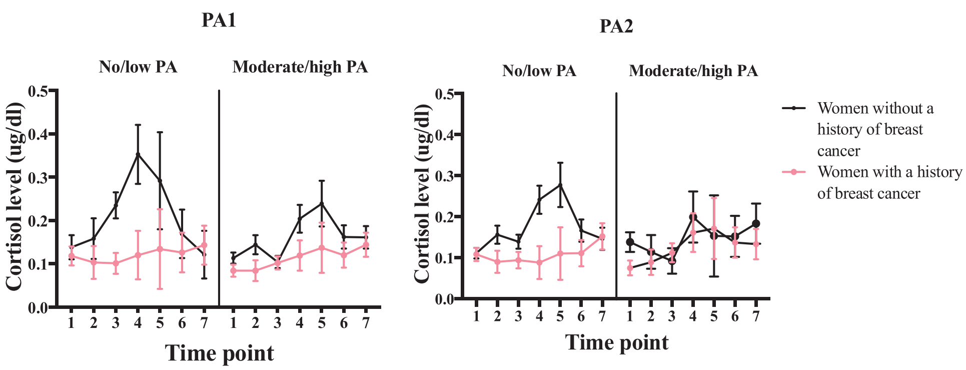

Fig. 4. Reactive cortisol profiles of participants with and without a history of cancer by aerobic PA frequency. On the left side (PA1), no/low PA shows participation in PA ≤ one time per week and moderate/high PA participation in PA ≥ two times per week. On the right side (PA2), no/low PA reflects participation in PA ≤ three times per week and moderate/high PA participation in PA ≥ four times per week. *1 = upon arrival; 2 = anticipation; 3 = arithmetic; 4 = 10 min after the Trier Social Stress Test (TSST); 5 = 20 min after the TSST; 6 = 40 min after the TSST; 7 = 60 min after the TSST.

4. Discussion

The specific objectives of the present study were to assess whether aerobic PA is associated with diurnal and reactive cortisol patterns, and whether the association between aerobic PA and cortisol patterns differed between women with and without a history of BC. In regards to our first objective, our hypothesis that women who engaged in aerobic PA more frequently (moderate/high PA group) would exhibit significantly less abnormalities in their cortisol patterns than those who engaged in aerobic PA less frequently or not at all (no/low PA group) was not supported as diurnal and reactive cortisol patterns did not differ statistically across aerobic PA groups. In regards to our second objective, a marginally significant ($p = .05$) cancer experience by aerobic PA interaction was observed when analyzing diurnal cortisol data suggesting that women without a history of BC who engaged in aerobic PA more frequently (moderate/high PA group) had a lower cortisol level at awakening and 30 min after awakening than women with a history of BC. Moreover, the association between aerobic PA and reactive cortisol patterns appeared to differ statistically based on women's cancer experience (i.e., history vs. no history of BC) when using the PA1 cutoff, whereby women without a history of BC had a significantly higher overall cortisol reactivity to an acute stressor (both in terms of AUCi and time point fluctuations) than women with a history of BC.

Others have also failed to detect a significant association between PA and cortisol patterns, regardless of history of cancer.[25,50] For example, similar to our findings, Payne et al.[25] did not find differences in diurnal cortisol levels between women in an exercise group comprised of home-based walking compared to women in a usual care group during hormonal treatment for BC. Yet, the authors did observe a downward trend for women in the exercise group compared to the usual care group, suggesting that women exposed to the exercise intervention ($n = 10$) had lower overall cortisol levels than women in the usual care group ($n = 10$). Nevertheless, the current evidence does not allow for conclusive inferences in favor of an association between PA and cortisol among women with a history of BC. It is possible that other factors or comorbid conditions may confound the association between PA and cortisol. First, cancer is often comorbid with several medication conditions that may impair cortisol regulation,[32–34] thus decreasing the effect of PA on cortisol regulation especially in those who experience severe medical conditions. Second, recent findings suggest that poor sleep may have powerful effects on the immune function and that it is a risk factor for impaired cortisol regulation.[51,52] Accordingly, as insomnia is common among women with a history of BC,[53,54] inflammatory responses to sleep deprivation may represent one mechanism affecting the association between PA and cortisol. Third, the biological mechanisms underlying the observed association between PA and cortisol in the general population are unclear.[40,41] It may be that alterations in hormonal responses caused by BC treatment compromise the beneficial effect of PA on cortisol among women with a history of BC. Thus, further research should include the simultaneous inclusion of a number of covariates known to be related to both PA and cortisol regulation.

It is important to note that our study, similar to others,[40] falls short of measuring PA parameters that may be implicated in the PA-cortisol association. Indeed, our PA measure was intended to provide an index of the total frequency of cardiovascular activities that raises a person's heart rate, but it lacks sensitivity to test whether intensity (e.g., light, moderate, vs. vigorous), duration (e.g., shorter long and continuous vs. short intervals), type (e.g., aerobic vs. anaerobic), context (e.g., indoors vs. outdoors or individual vs. group-based), and/or time of day moderates the association between PA and cortisol among women. For instance, many studies have suggested that increases in circulating cortisol levels are relatively proportional to PA intensity whereby a minimum intensity (i.e., threshold) is required in order to provoke a HPA response.[55–57] As the PA variable in our study was self-reported, we had no way to precisely measure whether PA intensity went above thresholds required to influence inflammatory responses. Moreover, other behavioural variables such sleep, sedentary time, fitness status, and food/beverage intake that may alter cortisol responses to PA[58–61] were also not considered (either due to limitations in sample size or because data were not collected). Future studies with direct assessments of PA (e.g., actigraphy) and more detailed PA questionnaires are needed, as well as better control for PA parameters and behavioural factors that could influence the association between PA and cortisol before firm conclusions can be made. Nevertheless, the effect sizes (based on the partial eta^2 values) in this study suggest that there is an association between aerobic PA frequency and cortisol patterns among women, which is critical as cortisol dysregulation is central to the etiology of several chronic conditions[23,30,31] and it would be valuable to determine which specific aspects of PA can be promoted to prevent this dysregulation. Over the years, researchers and statisticians have highlighted the importance of the use of effect sizes and explained why reporting *p*-values alone might not be enough in order to truly understand the results of a study.[62–66] Unlike *p*-values, effect sizes are not impacted by sample size and offer readers a quantitative index of the magnitude of the difference between groups. In the context of this study, consideration of the effect sizes in tandem with *p*-values give primordial interpretive information about the results that are not confounded with sample size. For that reason, we cannot discount the possibility that PA may still represent a protective factor for cortisol regulation and with a larger sample size, significant results might have emerged.[67]

Additionally, our results provide some evidence that aerobic PA may relate to cortisol patterns among women without a history of BC (Figs. 1 and 3). Albeit not statistically significant, the mean cortisol levels (diurnal and reactive) of women with a history of BC appear to remain fairly unchanged regardless of PA status (no/low vs. moderate/high PA group), whereas the mean cortisol levels of women without a history of BC who were included in the moderate/high PA group had lower levels than other women without a history of BC who were included in the no/low PA group. Although we hypothesized that more frequent engagement in aerobic PA may help to counter the negative physiological effect of a BC experience and that post-cancer cortisol dysregulation may be exacerbated by a lack of aerobic PA, collectively, our findings suggest that PA may not have the same effect on women with and without a cancer experience. Speculatively, fear of cancer recurrence, depression, overall stress, and fatigue which are common among women with a history of BC, might play a role in this relationship.[68,69] It seems necessary to further examine these mechanisms in larger samples as researchers have linked mortality rates of women with BC to the extent to which diurnal cortisol profiles deviate from the 'normal' pattern of cortisol secretion, thereby making cortisol dysregulation an important prognostic indicator of BC.[36,70] Indeed, whereas studies show that adults diagnosed with cancer who engage in PA regularly have lower risk of cancer recurrence,[2,7] this type of investigation may help shed light on one of the potential mechanisms through which PA exerts its effect.

5. Strengths and limitations

There are several limitations to this study. For instance, the small sample size significantly reduced the statistical power of the analyses and may explain our failure to obtain statistical significance. The self-report aerobic PA measure did not allow for the consideration of other factors such as duration and intensity that could influence the relationship between aerobic PA and cortisol. It is also important to consider that the prolonged duration of time since the BC treatment of our participants prevents generalization of our findings to women more recently diagnosed and treated for BC; thus findings are limited to long-term survivors.

This study has significant strengths as well. First, it is the first to examine the association between aerobic PA and cortisol patterns (diurnal and reactive) in women with and without a history of BC. Whereas in the current literature researchers have compared cortisol patterns between women with and without a history of BC,[26–28] very few have considered the role of PA.[40,41] Second, despite the recognition that diurnal and reactive cortisol are distinct,[23] few researchers have assessed both in relation to PA in the same participants in order to establish whether the relationship between PA and cortisol patterns is different for diurnal and reactive patterns. Third, the TSST was used to induce stress responses in participants; this protocol has repeatedly shown to yield sufficient HPA activity,[43,45,46] thereby allowing reliable and valid assessment of the cortisol reactivity profiles to be obtained from participants.

6. Conclusions

Although it is not possible to draw firm conclusions about the association between PA and cortisol patterns in women with and without a history of BC, examination of effect sizes indicates some relationship will require larger sample sizes to be explored more fully. Approximately 70% of women with a history of BC exhibit some dysregulation in their cortisol profile;[36,71] it is therefore crucial to further investigate modifiable lifestyle factors such as PA that could be used to counterbalance the negative physiological effects of BC. Encouraging women to engage in aerobic PA regularly may not only be effective in reducing subjective stress as shown in past studies,[13,14,21] but may also be used as a way to minimize physiological stress response dysregulation. Clearly, studies with larger sample sizes are warranted that include additional, more detailed self-report measures as well as direct assessments of PA in order to capture context, type, and intensity of PA and any covariates (e.g., behavioural factors, physical factors).

Conflict of interest

All authors certify no potential conflict of interest to disclose.

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