

REVIEW

# Cortisol Response in Breast Cancer: The Role of Physical Activity and Exercise

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ABSTRACT

Chronic stress is a consistent sense of feeling pressured and overwhelmed for a long period of time and it has been defined as a maladaptive state that is associated with altered hypothalamic pituitary adrenal (HPA) axis. The hyperactivity of the HPA axis is commonly assessed by cortisol levels. Physical activity (PA) and exercise have been demonstrated to regulate cortisol patterns in different healthy study populations, but also in BC patients and survivors. The PA and exercise are related but have distinct concepts that are commonly misused. Nowadays, the regular practice of PA and exercise has been widely recognized as one main strategy to manage chronic stress and its related markers, like cortisol, remains elusive. In the present review, the authors focused on the evidence of the PA and exercise on cortisol patterns of BC patients and survivors.

## 1. Introduction

Breast cancer (BC) is the leading cause of death in women, with diagnosis numbers growing each year<sup>[1]</sup>. Almost two million cases of BC were diagnosed in last years, according to the World Health Organization (WHO)<sup>[2]</sup>. Both non-pharmacological and pharmacological treat-

ments of BC can result in adverse side-effects at distinct levels, such as physical function, metabolic, cardiorespiratory and psychological<sup>[3,4]</sup>. These consequences may be associated with an interaction between pharmacological therapies and physiopathological and psychological conditions of each woman at the moment of diagnosis. After a diagnosis of BC, women experience emotional distress,

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depression and anxiety, which can persist for prolonged periods, irrespective of the clinical treatment outcome<sup>[5]</sup>.

Chronic stress is a consistent sense of feeling pressured and overwhelmed for a long period of time and it has been defined as a maladaptive state that is associated with altered immunity, hypothalamic pituitary adrenal (HPA) axis, and sympathetic nervous system (SNS) functioning<sup>[3]</sup>. Although research is still limited, the dysregulation of HPA axis and SNS, depression and anxiety have been reported in BC patients and survivors<sup>[5]</sup>. Studies show that almost 50% of BC patients experienced depression and/or anxiety during cancer treatments<sup>[4,6]</sup> and approximately 25% of women have clinically important levels of emotional distress up to 12 months after treatment<sup>[5]</sup>.

The hyperactivity of the HPA axis in response to a chronic stress is commonly assessed by cortisol awakening responses (CAR), i.e., the rapid increase in cortisol secretion roughly within the first 30 min of waking that of waking that occurs daily, signifying the physiological stress response to waking<sup>[7]</sup>. Cortisol levels are usually highest before awakening and decrease during the day<sup>[7]</sup>; however, the majority (>60%) of patients with BC show flattened circadian profiles, high levels, or unpredictable fluctuations<sup>[8,9]</sup>.

Physical activity (PA) and exercise have been recognized as a part of a healthy lifestyle, being associated with reduced risk of BC through several mechanisms, including by regulating sex-steroids hormones<sup>[10]</sup>, maintaining a healthy weight<sup>[11]</sup>, reducing inflammation<sup>[12]</sup>, and improving the immune response<sup>[13]</sup>. Some studies reported that PA and exercise were able to decrease levels of cortisol across different healthy study populations<sup>[14-16]</sup>. In the systematic review and meta-analysis conducted by De Nys et al.<sup>[17]</sup>, ten original studies were comprised including randomized controlled trial (RCTs) and non-RCTs with relevant control group. Here, they found moderate-certainty evidence for PA as an effective strategy in lowering cortisol levels in women with different clinical conditions. Although the PA and exercise are related they are distinct concepts that in this study were misused. In addition, the role of PA and exercise as beneficial strategy to manage chronic stress and its related markers, such as cortisol, remains elusive. In the present review, we focused on the evidence of the PA and exercise on cortisol fluctuations of BC patients and survivors.

## 2. Hypothalamic-pituitary-adrenal Axis in Response to Chronic Stress

In response to chronic stress, the physiologic mechanisms involve the neuroendocrine pathways constituting the SNS and HPA axis<sup>[3,4]</sup>. Both mechanisms are initiated

by releasing several neurotransmitters and hormones that influence behavioural and biochemical changes<sup>[18]</sup>. Under chronic stress, the brain's nerve impulses can continuously activate the hypothalamus to produce the corticotropin-releasing factor, which targets the pituitary gland. In its turn, pituitary gland releases the adrenocorticotropic hormone (ACTH)<sup>[19]</sup> that reaches the adrenal cortex by blood stream and promotes the synthesis of corticosteroids, including cortisol. In addition, SNS was triggered by chronic stress and, thus, stimulating the production and secretion of as norepinephrine and epinephrine, both known as catecholamines<sup>[18,19]</sup>. Both, corticosteroids and catecholamines, may contribute to a decline in the functions of the prefrontal cortex and the hippocampus, and may enhance the activation of the SNS and the HPA by regulating the expression of glucocorticoid receptors<sup>[18,20]</sup>.

A hyperactivation of the SNS and HPA axis in response to a chronic stress has been demonstrated to contribute, at least in part, for several cancer-promoting processes, such as tumorigenesis, progression, metastasis, and multi-drug resistance, by altering the tumour microenvironment (TME)<sup>[21]</sup>. A stressed TME is characterized by the increased proportion of cancer-promoting cells and cytokines, reduced and dysfunction of immune-supportive cells and cytokines, increased angiogenesis and epithelial-mesenchymal transition, as well as damaged extracellular matrix<sup>[19,21]</sup>. Of note that the enhanced  $\beta$ -adrenergic signalling and glucocorticoid signalling in TME can be induced by not only chronic, but also TME hypoxia<sup>[22]</sup>.

Several studies have been attributed associations between stress and cancers, such as prostate<sup>[23,24]</sup>, breast<sup>[25,26]</sup>, gastric<sup>[27]</sup> and lung<sup>[28]</sup>, suggesting that chronic stress can induce tumorigenesis and promote cancer development.

## 3. Cortisol

Cortisol is an adrenal hormone with many functions in the human body, such as mediating the stress response, regulating metabolism, inflammatory and immune functions<sup>[29]</sup>. Considering that cortisol is a glucocorticoid and the glucocorticoid receptors are present in almost tissue in the body, it affects nearly every organ system, including nervous, immune, cardiovascular, respiratory, reproductive, musculoskeletal muscle, and integumentary<sup>[29]</sup>.

Cortisol displays strong circadian rhythmicity, with high levels in the morning in the first 30-45 min after awakening, known as CAR and a gradual decline follows this peak during the waking day to reach the lowest levels at midnight<sup>[29]</sup>. This diurnal fluctuation is indicative of HPA axis reactivity<sup>[30]</sup>. Additionally, evidence has been demonstrated that salivary cortisol levels highly correlate with plasma and serum cortisol levels<sup>[31]</sup>.

## Cortisol Behaviour in Breast Cancer

BC patients and survivors likely have a dysregulation of the HPA axis and nonstandard secretion of cortisol, as previously demonstrated by [8,9]. Previous research demonstrated that BC survivors may experience significant alterations in their cortisol secretion patterns, as well as disruptions in the circadian rhythm of the HPA axis [9,32,33]. In the Obradović et al.'s study [33], the increase in glucocorticoids during BC progression was related to a lower survival rate, which is in agreement with a stimulatory effect of cortisol on cell proliferation observed in different cancer cell lines [27,34]. On the other hand, women with advanced BC and tamoxifen as first-line treatment presented significant elevations in basal cortisol levels compared to age-matched healthy women [8]. These findings suggest that BC is associated with a hyperactive adrenal gland, which may be due to the physiological stress associated with the presence of (micro)metastases or tumour cells in the circulation, in combination with administration of tamoxifen.

## 4. Physical Activity and Exercise

Although PA and exercise have been used confusingly, PA is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure.” [35] PA is closely related to, but distinct from exercise concept. Exercise is a subset of PA defined as “planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness.” [35].

Therefore, exercise practice has been widely recognized to improve cardiorespiratory fitness that positively affects health and self-efficacy [36], reduces insomnia-related distress [10] by improving nocturnal sleeping [37], and, consequently, body recovery [36,37]. At psychosocial

domain, exercise has several benefits, including favours interpersonal relations, which are important to attenuate depression and anxiety-related symptoms [38,39].

### 4.1 Effects of Physical Activity on Cortisol Levels in Breast Cancer

As shown in Table 1, only two studies studied the hypothetical association between PA and salivary cortisol [40,41]. Lambert et al. [40] found no associations in cortisol of physically activity BC women in post-treatment phase. On the other hand, Castonguay et al. [41] reported a decrease of salivary cortisol in 145 moderate-to-vigorous physically active BC women at least 12 months post-treatment. Both studies used healthy women without BC history as a comparator group. Taken together, these findings revealed that little is known about the role of PA in cortisol levels of BC women.

### 4.2 Effects of Exercise on Cortisol Levels in Breast Cancer

Regarding the effects of exercise intervention program on cortisol variations, controverse data exists, as seen in Table 2. Some of studies reported no changes after 14 weeks of home-based walking [42], 16 weeks of aerobic combined with strength exercise [43], 6 weeks of qigong [44], 3 weeks of dance movement therapy [45] or 48 weeks of supervised and unsupervised exercise sessions [46] in BC women.

Three studies used an exercise program where yoga classes were included with different period of time, one study lasted for 14 weeks [47] and two studies lasted for 6 weeks [48,49]. Ratcliff et al. [49] hypothesized that 6 weeks of yoga-based exercise intervention during radiotherapy would be beneficial for women with high baseline depressive symptoms compared with their counterparts par-

**Table 1.** Synthesis of studies evaluating the role of physical activity in BC women

Study Ref.:	Sample	Study Design	Main Finding
Castonguay et al. 2017 [41]	N=145 BC women post-treatment phase (≥12 months) Age: ≥ 18 years Comparator group: healthy women Country: Canada	PA was evaluated by leisure-time exercise questionnaire and then, combined the scores of the moderate and vigorous activities	Cortisol (salivar) ↓
Lambert et al. 2019 [40]	N=25 BC women post treatment phase (at least 6 months) Age: 57.9 years Comparator group: women without BC history Country: Canada	Self-reported PA frequency Participants were dichotomized into groups based on: ≤1x/week, 2-3x/week, 4-5x/week, 6-7x/week and ≥7x/week	Cortisol (salivar) ↔

**Table 2.** Synthesis of the effects of exercise in BC women

Study Ref.:	Sample	FIIT plan				Main Finding
		Frequency	Intensity	Time	Type	
Payne et al. 2008 [42]	N=10 BC post-menopausal women at post-treatment phase receiving hormonal therapy Age: 64.7±6.3, ranged 56 to 78 years Comparator group: usual care (n=10) Country: USA	4 x/week	Moderate, but without monitoring	20 min	Home-based walking exercise	Cortisol (serum) ↔
		During 14 weeks				
Banasik et al. 2010 [47]	N=9 BC women in post-treatment phase (≥2 months) Age: 63.33±6.9 years Comparator group: waitlist Country: USA	2 x/week	Not mentioned	90 min	Yoga classes	Cortisol (salivar) ↓ at morning and 5 p.m.
		During 14 weeks				
Chen et al. 2013 [44]	N=49 BC women had undergone breast surgery, and were scheduled to receive radiotherapy Age: 45.3±6.3, ranged 29 to 58 years Comparator group: waitlist receiving the clinical treatments Country: China	5x/week	Not mentioned	30-40 min	Qigong program	Cortisol (serum) ↔
		During 6 weeks				
Izzicupo P et al. (2013) [54]	N=32 BC in post-treatment phase Age: 56.38±4.33 Comparator group: (no access to full-text)	4x/week	Moderate (no reference what intensity parameter has been used)	40-50 min	Walking	Cortisol (plasma) ↔
		12 weeks				
Saxton et al. 2014 [55]	N= 44 overweight BC women at posttreatment phase (mean of 9.0±5.5) Age: 55.8±10.0 years Comparator group: control group received healthy eating booklet and advice to keeping active Country: UK	3x/week	65-85% age-predicted maximal heart rate	30 min	Aerobic followed by 10-15 min muscle strengthening exercises	Cortisol (salivar) ↑ at 8 a.m.

Table 2 continued

		Lifestyle intervention during 24 weeks: combination of exercise and hypocaloric diet				
Chandwani et al. 2014 <sup>[48]</sup>	N= 35 BC women had undergone breast surgery, and were scheduled to receive radiotherapy Age: 52.38±1.25, ranged 26 to 77 years Comparator group: stretching and waitlist Country: USA	3x/week	Not mentioned	60 min	Yoga classes	Cortisol (salivar) steeper slope ↓
		During 6 weeks				
Ratcliff et al. 2016 <sup>[49]</sup>	N=53 BC women had undergone breast surgery, and were scheduled to receive radiotherapy Age: ≥ 18 years Comparator group: stretching and waitlist Country: USA	3x/week	Not mentioned	60 min	Yoga classes	Cortisol (salivar) steeper slope ↓
		During 6 weeks				
Ho et al. 2016 <sup>[45]</sup>	N=72 BC women had undergone breast surgery, and were scheduled to receive radiotherapy Age: ≥ 18 years Comparator group: usual care Country: China	2x/week	Not mentioned	90 min	DMT	Cortisol (salivar) slope ↓
		During 3 weeks				
Evans et al. 2016 <sup>[50]</sup>	N=9 BC women in post-treatment phase Age: 50±6 VO <sub>2</sub> peak: 18.1±2.7 Comparator group: healthy women (without BC) Country: USA	1 bout of acute exercise	60% VO <sub>2</sub> peak was determined using Astrand cycle ergometer maximal test	30 min (10x3-min of exercise intercalated with 1.5 min of rest, for a total of 30 min of exercise in a 43.5-min period.	Aerobic and intermittent at cycle ergometer	Cortisol (plasma): ↓ post-exercise
Di Blasio et al. 2017	N= 33 BC women in post-treatment phase Age: 51.71±3.17 Comparator groups: i) healthy women and ii) physically active women Country: Italy	3x/week	1 <sup>st</sup> to 4 <sup>th</sup> week: 10 -11 RPE 5 <sup>th</sup> to 8 <sup>th</sup> week: 12 -13 RPE 9 <sup>th</sup> to 12 <sup>th</sup> : 13 -14 RPE	70 min	Nordic walking	Cortisol (salivar) negatively correlated with PA item Cortisol (salivar) ↓

Table 2 continued

		During 12 weeks				
Ho et al. 2018 [56]	N= 69 BC women had undergone breast surgery, and were scheduled to receive radiotherapy Age: 49.1±7.8 Comparator group: usual care receiving radiotherapy Country: China	2x/week	Not mentioned	Not mentioned	DMT	Cortisol (salivar) ↔ At high levels of baseline perceived stress, the DMT group showed a steeper cortisol slope
		During 3 weeks				
Friedenreich C et al. 2019 [46]	N=400 postmenopausal, physically inactive BC women were randomized into 2 groups: i) moderate-volume: 150 min/week or ii) high-volume: 300 min/week  Age: 59,6±5.1 years in moderate-volume group 59.4±4.9 years in high-volume group  VO <sub>2max</sub> : 26.8±4.9 mL/kg/min in moderate-volume group and 26.8±5.2 mL/kg/min in high-volume group	5x/week	70–80% heart rate reserve	Not mentioned	Not mentioned  3 supervised sessions and 2 unsupervised sessions	↔ between baseline vs. after 48 weeks and between groups
		During 48 weeks (1 year)				
Toohey K et al. 2020 [57]	N=17 BC and physically inactive women in post-treatment phase Age: 61±7.92 (control group); 65±7.68 (CMIT) and 60±8.12 (HIIT) Comparator group: waitlist Country: Australia	3x/week	50% of maximal power (watts) obtained in cycloergometer	HIIT: completed seven 30 s intervals (as hard as they could) with 2 min of active recovery between each. CMIT: 30 min	Aerobic exercise at cycloergometer	Cortisol (salivar) ↑, expressed as percent change from waking to 30 min post waking in HIIT group

Legend: HIIT: high-intensity interval training, CMIT: continuous and moderate-intensity training; PA: physical activity; DMT: dance movement therapy; RPE: rate of perceived exertion

participating in stretching or waitlist control groups. In this study, yoga group was associated with a steeper cortisol slope compared with stretching and waitlist groups. In this line, findings<sup>[39,48]</sup> support the idea that yoga intervention provided a huge mental health-related benefits for women with elevated sleep disturbance and, to a lesser extent, depressive symptoms prior to the start of radiotherapy. This effect varied in time with differences emerging especially 3 and 6 months after radiotherapy. Of note, some of these findings should be looked with some caution as the reduced reliability of cortisol slopes assessed at later follow-up points (because of a smaller sample size) may have limited the power to detect the effects of cortisol slopes<sup>[49]</sup>. Moreover, two of these<sup>[48,49]</sup> studies have assessed salivary cortisol after chemotherapy and during the radiotherapy, excluding other treatments phases. Interestingly, no study has studied the effects of exercise on cortisol variations during diagnosis, chemotherapy or after surgery.

In an exploratory investigation, Evans et al. (2016)<sup>[50]</sup> aimed to study the effects of one bout of acute exercise on plasma cortisol in BC women in post-treatment phase. Although healthy women without BC history have been used as a comparator group, both groups (intervention and comparator) display identical body index mass, oxygen requirements (18.1±2.7 vs. 18.5±0.83 mL O<sub>2</sub>/min/kg, workload (107±19 vs. 106±17 watts), heart rate (68±6 vs. 66±9 bpm) and RPE (12±1 vs. 12±1). This point is very pertinent as the responsiveness of stress hormones is directly proportional to physical and physiological demands of the body<sup>[51]</sup>. This study brings novel findings demonstrating that cortisol levels changed across time in the BC survivor group with a decrease immediately after exercise session cessation, but without significant changes after 2 h. The intermittent nature of the exercise training protocol may have stimulated the metabolic and hormonal responses differently than continuous exercise, which explain partly the unexpected cortisol variations. Therefore, the implementation of exercise programs with these characteristics (i.e., intercalated with high-intense periods with low-to-moderate periods of exercise) specially in BC patients/survivors are utmost importance to know the potentially of this exercise type.

Exercise-induced fluctuations in plasma cortisol levels typically follow a threshold effect in which exercise at ≥60% of maximal oxygen consumption (VO<sub>2</sub>max) of intensity induce increased plasma cortisol concentrations<sup>[51]</sup>. However, in the Evans's study<sup>[50]</sup> the intensity prescription was based on VO<sub>2</sub> peak, which is usually slightly lower than VO<sub>2</sub>max. Thus, 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<sup>[50]</sup>. Another important factor that may help to explain the Evan's findings could be the suppressive role of selective estrogens receptor modifiers, such as Tamoxifen, on adrenal corticosteroids release<sup>[52]</sup>. In fact, Tamoxifen is a selective estrogen receptor modulator widely used in adjuvant therapy for estrogen receptor-positive BC<sup>[53]</sup>. Considering that BC women generally received chemotherapy and, thereafter, intake hormonal therapy medication, some controverser results may be in part due to the use of current medication.

## 5. Conclusions

Based on compelling data from studies, the current state of knowledge supports that PA and exercise are interventions that should be included in a BC women's health care program due to their fundamental role in chronic stress management. Although few studies suggest a beneficial effect of exercise in cortisol of BC women during or after radiotherapy, no study has considered other cancer treatments phases. Future studies are warranted to address the effects of PA and also exercise on cortisol patterns of BC women at different cancer treatments phases, along with chronic stress evaluation and other psychological parameters.

## Disclosure Statement

The authors do not have any financial interest and did not receive any financial benefit from this research.

## Conflict of Interest

The authors state no conflict of interest.

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