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

Margarida Marinho¹  Sílvia Rocha-Rodrigues¹,²*

¹. Escola Superior de Desporto e Lazer, Instituto Politécnico de Viana do Castelo, Rua Escola Industrial e Comercial de Nun’Alvares, 4900-347 Viana do Castelo, Portugal
². Tumour & Microenvironment Interactions Group, INEB- Institute of Biomedical Engineering, i3S-Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Rua Alfredo Allen, 208, 4200-153 Porto, Portugal

ARTICLE INFO

Article history
Received: 1 August 2022
Revised: 31 August 2022
Accepted: 1 September 2022
Published Online: 13 September 2022

Keywords:
Physically active
Chronic stress
Depression
Cancer
Women

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 [1]. Almost two million cases of BC were diagnosed in last years, according to the World Health Organization (WHO) [2]. Both non-pharmacological and pharmacological treatments of BC can result in adverse side-effects at distinct levels, such as physical function, metabolic, cardiorespiratory and psychological [3,4]. 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,
depression and anxiety, which can persist for prolonged periods, irrespective of the clinical treatment outcome [5].

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 [3]. Although research is still limited, the dysregulation of HPA axis and SNS, depression and anxiety have been reported in BC patients and survivors [5]. Studies show that almost 50% of BC patients experienced depression and/or anxiety during cancer treatments [4,8] and approximately 25% of women have clinically important levels of emotional distress up to 12 months after treatment [5].

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 occurs daily, signifying the physiological stress response to waking [7]. Cortisol levels are usually highest before awakening and decrease during the day [7]; however, the majority (>60%) of patients with BC show flattened circadian profiles, high levels, or unpredictable fluctuations [9,9].

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 [10], maintaining a healthy weight [11], reducing inflammation [12], and improving the immune response [13]. Some studies reported that PA and exercise were able to decrease levels of cortisol across different healthy study populations [14-16]. In the systematic review and meta-analysis conducted by De Nys et al. [17], 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 [7,4]. Both mechanisms are initiated by releasing several neurotransmitters and hormones that affluence behavioural and biochemical changes [18]. Under chronic stress, the brain’s nerve impulses can continuously activate the hypothalamus to produce the corticotropin-releasing factor, which is targets the pituitary gland. In its turn, pituitary gland releases the adrenocorticotropic hormone (ACTH) [19] 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 norepinephrine and epinephrine, both known as catecholamines [18,19]. 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 [18,20].

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) [21]. 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 [19,21]. Of note that the enhanced β-adrenergic signalling and glucocorticoid signalling in TME can be induced not only by chronic, but also TME hypoxia [22].

Several studies have been attributed associations between stress and cancers, such as prostate [23,24], breast [25,26], gastric [27] and lung [28], 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 [29]. 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 [29].

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 [29]. This diurnal fluctuation is indicative of HPA axis reactivity [30]. Additionally, evidence has been demonstrated that salivary cortisol levels highly correlate with plasma and serum cortisol levels [31].
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 active 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, controversial 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) ↓ |
| | 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 |
|-------------|--------|-----------|--------------|
| 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) ↔ during 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. during 24 weeks |
Lifestyle intervention during 24 weeks: combination of exercise and hypocaloric diet

| Reference | Study Details | Intervention Details | Comparator Group | Country | Duration | PA Item | Cortisol Change |
|-----------|---------------|----------------------|------------------|---------|----------|---------|-----------------|
| Chandwani et al. 2014 [48] | 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 ↓ |
| Ratcliff et al. 2016 [49] | 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 ↓ |
| Ho et al. 2016 [40] | 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 ↓ |
| Evans et al. 2016 [50] | N=9 BC women in post-treatment phase Age: 50±6 VO₂ peak: 18.1±2.7 Comparator group: healthy women (without BC) Country: USA | 1 bout of acute exercise | 60% VO₂ 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 | 1st to 4th week: 10 -11 RPE 5th to 8th week: 12 -13 RPE 9th to 12th: 13 -14 RPE | 70 min | Nordic walking | Cortisol (salivar) negatively correlated with PA item | Cortisol (salivar) ↓ |
| Study | Duration | Sample Description | Intervention Details | Comparator | Outcomes |
|-------|----------|--------------------|----------------------|------------|----------|
| Ho et al. 2018 [56] | 12 weeks | N= 69 BC women had undergone breast surgery, and were scheduled to receive radiotherapy | 2x/week Not mentioned Not mentioned DMT | Cortisol (salivar) ↔ At high levels of baseline perceived stress, the DMT group showed a steeper cortisol slope |
| Friedenreich C et al. 2019 [46] | 3 weeks | 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 | 5x/week 70–80% heart rate reserve Not mentioned Not mentioned ↔ between baseline vs. after 48 weeks and between groups |
| Toohey K et al. 2020 [57] | 48 weeks (1 year) | N=17 BC and physically inactive women in post-treatment phase | 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
ticipating 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 [39,48] 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 [49]. Moreover, two of these [48,49] 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) [50] 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 O2/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 [51]. 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 (VO2max) of intensity induce increased plasma cortisol concentrations [51]. However, in the Evans’s study [50] the intensity prescription was based on VO2 peak, which is usually slightly lower than VO2max. 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 [50]. 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 [52]. In fact, Tamoxifen is a selective estrogen receptor modulator widely used in adjuvant therapy for estrogen receptor-positive BC [53]. Considering that BC women generally received chemotherapy and, thereafter, intake hormonal therapy medication, some controversy 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.

References

[1] Siegel, R.L., Miller, K.D., Jemal, A., 2019. Cancer statistics. Ca A Cancer Journal for Clinicians. 1(1), 7-34. DOI: https://doi.org/10.3322/caac.21551
[2] Mattiuzzi, C., Lippi, G., 2020. Cancer statistics: a comparison between World Health Organization (WHO) and Global Burden of Disease (GBD). European Journal of Public Health. 1(5), 1026-1027. DOI: https://doi.org/10.1093/eurpub/ckz216
[3] Cuevas, B.T., Hughes, D.C., Parma, D.L., et al., 2014. Motivation, exercise, and stress in breast cancer survivors. Support Care Cancer. 4, 911-917. DOI: https://doi.org/10.1007/s00520-013-2038-6
[4] Botto, R., Leonards, B.D., Salussolia, A., et al., 2022. Assessment of anxiety, depression, and dis-
stress in breast cancer patients: A comparison among different phases of illness. Health Care for Women International. 1-13.
DOI: https://doi.org/10.1080/07399332.2022.2078325

[5] Sanchez, L., Fernandez, N., Calle, A.P., et al., 2019. Long-term treatment for emotional distress in women with breast cancer. European Journal of Oncology Nursing. 126-133.
DOI: https://doi.org/10.1016/j.ejon.2019.09.002

[6] Phoosuwan, N., Lundberg, P.C., 2022. Psychological distress and health-related quality of life among women with breast cancer: a descriptive cross-sectional study. Supportive Care in Cancer. 4, 3177-3186.
DOI: https://doi.org/10.1007/s00520-021-06763-z

[7] Wüst, S., Wolf, J., Hellhammer, D.H., et al., 2000. The cortisol awakening response - normal values and confounds. Noise Health. 7, 79-88.

[8] van der Pompe, G., Antoni, M.H., Heijnen, C.J., 1996. Elevated basal cortisol levels and attenuated ACTH and cortisol responses to a behavioral challenge in women with metastatic breast cancer. Psychoneuroendocrinology. 4, 361-374.
DOI: https://doi.org/10.1016/0306-4530(96)00009-1

[9] Touitou, Y., Bogdan, A., Benavides, M., et al., 1996. Disruption of the circadian patterns of serum cortisol in breast and ovarian cancer patients: relationships with tumor marker antigens. British Journal of Cancer. 8, 1248-1252.
DOI: https://doi.org/10.1038/bjc.1996.524

[10] Rocha-Rodrigues, S., 2021. Physical exercise and sex steroid hormones in breast cancer. Human Movement. 2, 1-8.
DOI: https://doi.org/10.5114/hm.2021.100006

[11] Jia, T.T., Liu, Y.F., Fan, Y.Y., et al., 2022. Association of Healthy Diet and Physical Activity With Breast Cancer: Lifestyle Interventions and Oncology Education. Front Public Health. 797794.
DOI: https://doi.org/10.3339/fpubh.2022.797794

[12] Lee, K.J., An, K.O., 2022. Impact of High-Intensity Circuit Resistance Exercise on Physical Fitness, Inflammation, and Immune Cells in Female Breast Cancer Survivors: A Randomized Control Trial. International Journal of Environmental Research and Public Health. 9.
DOI: https://doi.org/10.3390/ijerph19095463

[13] Enayatjazi, M., Esfarjani, F., Reisi, J., et al., 2022. Studying the Effect of Garlic Consumption and Endurance Training on Serum Levels of Some Pro-and Anti-inflammatory Cytokines in Female Mice with Breast Cancer - A Randomized Trial. International Journal of Preventive Medicine. 13(1), 38.
DOI: https://doi.org/10.4103/ijpvm.IJPM_315_20

[14] Corazza, D.I., Sebastião, É., Pedroso, R.V., et al., 2014. Influence of chronic exercise on serum cortisol levels in older adults. European Review of Aging and Physical Activity. 1, 25-34.
DOI: https://doi.org/10.1010/s11556-013-0126-8

[15] Laugero, K.D., Falcon, L.M., Tucker, K.L., 2011. Relationship between perceived stress and dietary and activity patterns in older adults participating in the Boston Puerto Rican Health Study. Appetite. 1, 194-204.
DOI: https://doi.org/10.1016/j.appet.2010.11.001

[16] Hayes, L.D., Grace, F.M., Baker, J.S., et al., 2015. Exercise-induced responses in salivary testosterone, cortisol, and their ratios in men: a meta-analysis. Sports Medicine. 5, 713-726.
DOI: https://doi.org/10.1010/s40279-015-0306-y

[17] De Nys, L., Anderson, K., Ofosu, E.F., et al., 2022. The effects of physical activity on cortisol and sleep: A systematic review and meta-analysis. Psychoneuroendocrinology. 143, 105843.
DOI: https://doi.org/10.1016/j.psyneuen.2022.105843

[18] Smith, S.M., Vale, W.W., 2006. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues in Clinical Neuroscience. 4, 383-395.
DOI: https://doi.org/10.31887/DCNS.2006.8.4/ssmith

[19] Wendel, J., Verma, A., Dhevan, V., et al., 2021. Stress and Molecular Drivers for Cancer Progression: A Longstanding Hypothesis. Biomedical Journal of Scientific and Technical Research. 1, 29134-29138.
DOI: https://doi.org/10.26717/bjstr.2021.37.005953

[20] Arnsten, A.F., 2015. Stress weakens prefrontal networks: molecular insults to higher cognition. Nature Neuroscience. 10, 1376-1385.
DOI: https://doi.org/10.1038/nn.4087

[21] Tian, W.T., Liu, Y., Cao, Ch.H., et al., 2021. Chronic Stress: Impacts on Tumor Microenvironment and Implications for Anti-Cancer Treatments. Frontiers in Cell and Developmental Biology. 777018.
DOI: https://doi.org/10.3389/fcell.2021.777018

[22] Chiarugi, P., Filippi, L., 2015. β3-adrenoreceptor and tumor microenvironment: a new hub. Oncoimmunology. 4, 361-374.

[23] Hayes, L.D., Grace, F.M., Baker, J.S., et al., 2015. Stress and Molecular Drivers for Cancer Progression: A Longstanding Hypothesis. Biomedical Journal of Scientific and Technical Research. 1, 29134-29138.
DOI: https://doi.org/10.26717/bjstr.2021.37.005953

[24] Flores, I.E., Sierra, F.J.A., Davalos, O., et al., 2017. Stress and Molecular Drivers for Cancer Progression: A Longstanding Hypothesis. Biomedical Journal of Scientific and Technical Research. 1, 29134-29138.
Stress alters the expression of cancer-related genes in the prostate. BMC Cancer. 1, 621.
DOI: https://doi.org/10.1186/s12885-017-3635-4

[25] Bowen, D., Poole, S.F., White, M., et al., 2021. The Role of Stress in Breast Cancer Incidence: Risk Factors, Interventions, and Directions for the Future. International Journal of Environmental Research and Public Health. 4.
DOI: https://doi.org/10.3390/ijerph18041871

[26] Sistigu, A., Musella, M., Galassi, C., et al., 2020. Tuning Cancer Fate: Tumor Microenvironment’s Role in Cancer Stem Cell Quiescence and Reawakening. Frontiers in Immunology. 2166.
DOI: https://doi.org/10.3389/fimmu.2020.02166

[27] Zhang, X., Zhang, Y., He, Z., et al., 2019. Chronic stress promotes gastric cancer progression and metastasis: an essential role for ADRB2. Cell Death and Disease. 11, 788.
DOI: https://doi.org/10.1038/s41419-019-2030-2

[28] Jafri, S.H., Ali, F., Mollaeeian, A., et al., 2019. Major Stressful Life Events and Risk of Developing Lung Cancer: A Case-Control Study. Clinical Medicine Insights Oncology. 1179554919835798.
DOI: https://doi.org/10.1177/1179554919835798

[29] Kadmiel, M., Cidlowski, J.A., 2013. Glucocorticoid receptor signaling in health and disease. Trends in Pharmacology Sciences. 9, 518-530.
DOI: https://doi.org/10.1016/j.tips.2013.07.003

[30] Smyth, J.M., Ockenfels, M.C., Gorin, A.A., et al., 1997. Individual differences in the diurnal cycle of cortisol. Psychoneuroendocrinology. 2, 89-105.
DOI: https://doi.org/10.1016/s0306-4530(96)00039-x

[31] Lee, D.Y., Kim, E., Choi, M.H., 2015. Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. BMB Reports. 4, 209-216.
DOI: https://doi.org/10.5483/bmbrep.2015.48.4.275

[32] Spiegel, D., Giese-Davis, J., Taylor, C.B., et al., 2006. Stress sensitivity in metastatic breast cancer: analysis of hypothalamic-pituitary-adrenal axis function. Psychoneuroendocrinology. 10, 1231-1244.
DOI: https://doi.org/10.1016/j.psyneuen.2006.09.004

[33] Obradović, M.M.S., Hamelin, B., Manevski, N., et al., 2019. Glucocorticoids promote breast cancer metastasis. Nature. 7749, 540-544.
DOI: https://doi.org/10.1038/s41586-019-1019-4

[34] Zhao, X.Y., Malloy, P.J., Krishnan, A.V., et al., 2000. Glucocorticoids can promote androgen-independent growth of prostate cancer cells through a mutated androgen receptor. Nature Medicine. 6, 703-706.
DOI: https://doi.org/10.1038/76287

[35] Caspersen, C.J., Powell, K.E., Christenson, G.M., 1985. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Reports. 2, 126-131.

[36] Ficarra, S., Thomas, E., Bianco, A., et al., 2022. Impact of exercise interventions on physical fitness in breast cancer patients and survivors: a systematic review. Breast Cancer. 3, 402-418.
DOI: https://doi.org/10.1007/s12282-022-01347-z

[37] Yang, H.Ch., Yang, Zh., Pan, H.Y., et al., 2021. Effects of physical activity on sleep problems in breast cancer survivors: a meta-analysis. Support Care Cancer. 7, 4023-4032.
DOI: https://doi.org/10.1007/s00520-020-05914-y

[38] Marinho, M.S., Rocha-Rodrigues, B.S., 2021. Depression And Quality Of Life In Physically Active Breast Cancer Survivors. Proceedings of XVI International Conference in Physical Education, Leisure and Health. 49.

[39] Di Blasio, A., Morano, T., Cianchetti, E., et al., 2017. Psychophysical health status of breast cancer survivors and effects of 12 weeks of aerobic training. Complementary Therapies in Clinical Practice. 19-26.
DOI: https://doi.org/10.1016/j.ctcp.2017.01.004

[40] Lambert, M., Brunet, J., Couture-Lalande, M.E., et al., 2019. Aerobic physical activity and salivary cortisol levels among women with a history of breast cancer. Complementary Therapies in Medicine. 12-18.
DOI: https://doi.org/10.1016/j.ctim.2018.10.018

[41] Castonguay, A.L., Wrosch, C., Sabiston, C.M., 2017. The roles of negative affect and goal adjustment capacities in breast cancer survivors: Associations with physical activity and diurnal cortisol secretion. Health Psychology. 4, 320-331.
DOI: https://doi.org/10.1037/heo0000477

[42] Payne, J.K., Held, J., Thorpe, J., et al., 2008. Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncology Nursing Forum. 4, 635-642.
DOI: https://doi.org/10.1188/08.Onf.635-642

[43] Arikawa, A.Y., Thomas, W., Patel, S.R., et al., 2013. No effect of exercise on urinary 6-sulfatoxymelatonin and catecholamines in young women participating in a 16-week randomized controlled trial. Cancer Epidemiology, Biomarkers and Prevention. 9, 1634-1636.
DOI: https://doi.org/10.1158/1055-9965.Epi-13-0583

[44] Chen, Z., Meng, Z., Milbury, K., et al., 2013. Qigong improves quality of life in women undergoing radiotherapy for breast cancer: results of a randomized
controlled trial. Cancer. 9, 1690-1698.
DOI: https://doi.org/10.1002/cncr.27904

[45] Ho, R.T., Fong, T.C.T., Cheung, I.K.M., et al., 2016. Effects of a Short-Term Dance Movement Therapy Program on Symptoms and Stress in Patients With Breast Cancer Undergoing Radiotherapy: A Randomized, Controlled, Single-Blind Trial. Journal of Pain Symptom Manage. 5, 824-831.
DOI: https://doi.org/10.1016/j.jpainsymman.2015.12.332

[46] Friedenreich, C.M., Wang, Q., Shaw, E., et al., 2019. The effect of prescribed exercise volume on biomarkers of chronic stress in postmenopausal women: Results from the Breast Cancer and Exercise Trial in Alberta (BETA). Preventive Medicine Reports. 100960.
DOI: https://doi.org/10.1016/j.jpmedr.2019.100960

[47] Banasik, J., Williams, H., Haberman, M., et al., 2011. Effect of iyengar yoga practice on fatigue and diurnal salivary cortisol concentration in breast cancer survivors. Journal of the American Academy of Nurse Practice. 3, 135-142.
DOI: https://doi.org/10.1111/j.1745-7599.2010.00573.x

[48] Chandwani, K.D., Perkins, G., Nagendra, H.R., et al., 2014. Randomized, controlled trial of yoga in women with breast cancer undergoing radiotherapy. Journal of Clinical Oncology. 10, 1058-1065.
DOI: https://doi.org/10.1200/jco.2012.48.2752

[49] Ratcliff, C.G., Milbury, K., Chandwani, K.D., et al., 2016. Examining Mediators and Moderators of Yoga for Women With Breast Cancer Undergoing Radiotherapy. Integrative Cancer Therapies. 3, 250-262.
DOI: https://doi.org/10.1177/153475415624141

[50] Oppermann, H., Dulz, A., Helmeke, C., et al., 2016. Adrenal Hormone and Metabolic Biomarker Responses to 30 min of Intermittent Cycling Exercise in Breast Cancer Survivors. International Journal of Sports Medicine. 12, 921-929.
DOI: https://doi.org/10.1055/s-0042-110654

[51] McMurray, R.G., 1993. Exercise and Sport Science Reviews, Volume 21 JO Holloszy,(Ed.). LWW.

[52] Genazzani, A.R., Lombardi, I., Borgioli, G., et al., 2003. Adrenal function under long-term raloxifene administration. Gynecological endocrinology. 2, 159-168.

[53] An, K.C., 2016. Selective Estrogen Receptor Modulators. Asian Spine Journal. 4, 787-791.
DOI: https://doi.org/10.4184/asj.2016.10.4.787

[54] Izzicupo, P., D’Amico, M.A., Bascelli, A., et al., 2013. Walking training affects dehydroepiandrosterone sulfate and inflammation independent of changes in spontaneous physical activity. Menopause. 4, 455-463.
DOI: https://doi.org/10.1097/gme.0b013e31827425c9

[55] Saxton, J.M., Scott, E.J., Daley, A.J., et al., 2014. Effects of an exercise and hypocaloric healthy eating intervention on indices of psychological health status, hypothalamic-pituitary-adrenal axis regulation and immune function after early-stage breast cancer: a randomised controlled trial. Breast Cancer Research. 2, R39.
DOI: https://doi.org/10.1186/bcr3643

[56] Ho, R.T.H., Fong, T.C.T., Yip, P.S.F., 2018. Perceived stress moderates the effects of a randomized trial of dance movement therapy on diurnal cortisol slopes in breast cancer patients. Psychoneuroendocrinology. 119-126.
DOI: https://doi.org/10.1016/j.psyneuen.2017.10.012

[57] Toohey, K., Pumpa, K., McKune, A., et al., 2020. The impact of high-intensity interval training exercise on breast cancer survivors: a pilot study to explore fitness, cardiac regulation and biomarkers of the stress systems. BMC Cancer. 1(1), 787.
DOI: https://doi.org/10.1186/s12885-020-07295-1