Differences in Heart Rate Variability and Body Composition in Breast Cancer Survivors and Women Without Cancer

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Abstract

Purpose: To explore cardiac autonomic changes assessed by linear and nonlinear indexes of heart rate variability (HRV) and body composition modifications in breast cancer survivors and cancer-free control women.

Methods: Women who were breast cancer survivors (BCS, *n*=27) and cancer-free control participants with similar characteristics (Control, *n*=31) were enrolled in the Regional General Hospital No. 251 of the Mexican Institute of Social Security (Metepec, Mexico). We processed five minutes of R-R interval time series, and we calculated relevant linear and nonlinear parameters of HRV such as mean RR interval (RRa_{ve}), the Root Mean Square of the Successive Differences (RMSSD), the Poincaré plot measures SD1, SD2, SD1/SD2, and the sample entropy (SampEn). Additionally, we indirectly assessed body composition measures such as body weight, fat mass, visceral fat rating (VFR), normalized VRF (nVFR), muscle mass, metabolic age, and total body water.

Results: We found that diverse HRV indexes and only one body composition measure showed statistical differences ($p<0.05$) between the BCS and Control groups: RRa_{ve}: 729 (648–802) vs. 795 (713–852) ms; RMSSD: 16.5 (8.9–27.0) vs. 19.7 (14.2–28.5) ms; SD1: 11.6 (6.3–19.0) vs. 13.9 (10.0–20.1) ms; SD1/SD2: 2.5 (2.1–3.3) vs. 2.2 (1.9–2.7), SampEn: 1.5 (1.3–1.8) vs. 1.7 (1.5–1.8), and nVFR 0.12 (0.11–0.13) vs.0.10 (0.08–0.12) points/kg, respectively. The nVFR was significantly correlated to several indexes of HRV.

Conclusions: BCS exhibit a lower parasympathetic cardiac activity and changes in HRV patterns than controls, likely because of the concomitant increase of visceral fat.

Introduction

Breast cancer is among the five most common forms of cancer, and it is one of the most important causes of death worldwide, accounting for an estimated 627 000 deaths in 2018 [1]. In Latin America, breast cancer ranks as the first cancer type among women regarding new cases and deaths [2]. Studies indicate that women who are breast cancer survivors (BCS) show a stronger association with metabolic syndrome [3], diabetes [4], and abdominal obesity [5], which are major risk factors for cardiovascular disease [6].

Body composition in breast cancer management seems to be a factor of interest in and refers to the amount and distribution of lean tissue and adipose tissue in the patients [7]. Interestingly, the study of body composition has been considered as one of the most promising areas in oncology [8]. Evidence suggests that it is a crucial contributor to clinical outcomes after breast cancer surgery [9]. Potential factors, such as metabolic dysregulation and weight gain, are associated with autonomic dysfunction and increased cardiovascular disease risk in patients with breast cancer [10].

Autonomic dysfunction is known to be expected in various types of cancer and leads to increased sympathetic activity and decreased vagal tone in the heart [11]. BCS may also show an autonomic impairment due to adjuvant therapies [12], among other factors. Furthermore, findings suggest that BCS show decreased sympathetic and parasympathetic activity than women without cancer [13]. BCS exhibit numerous dysfunctions: vagal impairment, lower aerobic fitness, signs of altered metabolism, and higher perception of fatigue [14].

The heart rate variability (HRV) analysis has been established as a complementary non-invasive and economical tool for the early diagnosis and better prognosis of autonomic cardiac dysfunction and survival in BCS women [15].

Studies have shown that the presence of a cardiovascular imbalance in BCS in comparison to healthy controls, suggesting that traditional linear indexes of HRV study could be clinically useful to detect cardiovascular disease in BCS [16]. Promising nonlinear tools have been introduced to describe the complexity of HRV, which presents the advantage of not being affected by nonstationary effects than typical linear HRV indexes [17]. The nonlinear methods have shown great promise in the detection and diagnosis of heart failure [18]. However, in BCS, the nonlinear properties of cardiac dynamics related to changes in the autonomic nervous system (ANS) and complexity have not been fully elucidated.

Changes in body composition may lead to modifications in the autonomic cardiac function [19]. Data indicate that physical training can reverse impaired cardiorespiratory fitness and autonomic modulation in women with breast cancer receiving adjuvant therapy [20].

To our knowledge, no other studies have compared autonomic cardiac activity assessed by linear and nonlinear HRV measures in conjunction with various measures of body composition values between BCS and cancer-free women. With this background, this study aims to assess the autonomic cardiac function and body composition modifications in BCS and women with no cancer diagnosis under similar characteristics. We hypothesized that women who are BCS manifest cardiac autonomic disturbances related to changes in body composition.

Methods

Study design

In this cross-sectional study, Mexican women between 30 and 67 years old who attended the Oncology Service at the Regional General Hospital No. 251 of the Mexican Institute of Social Security (Metepec, Mexico State, Mexico), from March 2019 until July 2019 were invited to participate in this study. The BCS group included women who were in their post-cancer follow-up appointment. The inclusion criteria included the following: a) previous diagnosis of breast cancer; b) women who had undergone breast cancer surgery (lumpectomy or mastectomy) anywhere from one year to five years earlier and women who did not require surgery; b) no evidence of metastases, c) absence of respiratory and cardiovascular diseases, diabetes mellitus, thyroid dysfunction, hypertension; d) normotensive; e) capacity to stand up unaided, and f) capacity to answer a clinical interview, including a familiar history of cancer. The exclusion criteria consisted of the following: a) women under anticancer medication (e.g., tamoxifen [21]) or any other medication; b) women undergoing chemotherapy or radiotherapy and c) super-obese women (BMI>50 kg/m^2) and d) smoking. The elimination criteria involved women who presented RR time series with an error greater than 5% were excluded from the study.

Moreover, the control group included women without diagnosis of cancer with similar characteristics to the BCS group (ethnicity, age, weight, BMI, and height). In all controls, the presence of chronic diseases or pharmacological treatment was excluded by history and standard medical examination.

The sample size estimation was based on the study of Romanholi Palma et al. [13] and was determined using the G*Power software [22]. We considered an 80% test power, an alpha error of 5% for a one-tailed test. The minimum sample size was determined to be 14 participants per group.

Electrocardiogram recording and preprocessing

On the day of the study, all participants arrived in the Oncology service, having avoided caffeinated or alcoholic beverages. Electrophysiological recordings were performed between 08:00 and 12:00 am to account for circadian rhythms of the heartbeat. All participants were asked to relax and record in a standard seated position at rest [23]. The first lead (DI) of the electrocardiogram (ECG) was recorded for 5 minutes by using an ECG sensor model EKG-BTA (Vernier®, Beaverton, Oregon, USA) for NI Elvis II (Texas Instruments®, Dallas, Texas, USA) and superficial disposable electrodes. Electrocardiographic data were acquired with a PC at a sampling rate of 1000 Hz using the Biosignal Logger and Player software (National instruments®, Austin, Texas, USA).

Raw ECG recordings for both BCS and Control groups were then processed using previously validated algorithms to generate RR time series [24]. All the RR time series were reconditioned by a filtering approach and tested in line with previous studies to exclude ectopic beats [25]. All these calculations were obtained using Matlab® software (the MathWorks, Inc. Natick, Massachusetts, USA).

Heart rate variability (HRV) assessment

We assessed HRV according to methodological standards proposed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology for HRV [26]. We used the Kubios software version 3.1 (Kuopio, Finland) [25] to analyze RR time series. The following linear (time-domain) indexes were included: R-R interval (RRave), the standard deviation of the RR time series of normal sinus beats (SDNN, a biomarker of global HRV), the root mean square of successive differences (RMSSD), and the percentage of pairs of successive RR intervals that differ by more than 50 ms, these last two biomarkers are associated to the cardiac parasympathetic function [26].

Linear (frequency-domain) indexes were also reported: normalized low-frequency (LFnu: 0.04–0.15 Hz) and high-frequency (HFnu: 0.15–0.4 Hz). HFnu index is a parasympathetic modulation indicator, while LFnu is a general indicator of both the sympathetic and parasympathetic modulation branches of the ANS [27]. By default, a 4 Hz interpolation was set in the Kubios software. The spectrum for the selected RR time series was computed with Welch's periodogram method (FFT spectrum). The default value for window width was 256 seconds, and the default overlap was 50 % [28].

Furthermore, we performed a nonlinear analysis of HRV. We considered the Poincaré indexes SD1, SD2, and SD1/SD2. SD1 is an index of short-term variability and reflects parasympathetic activity, while the SD2 index measures the long-term variability and reflects the overall variability. The (SD1/SD2) ratio represents the balance between long- and short-term HRV [29]. The quantitative analysis of a plot involves fitting an ellipse to the Poincaré plot, which corresponds to the length of the minor (SD1) and major (SD2) axes. Besides that, we measured the short-term fractal exponent (α_1), corresponding to a period of 4 to 11 beats, and the long-term fractal exponent (α_2), corresponding to periods longer than 11 beats [30]. When $\alpha = 0.05$, there is no correlation, and the time series shows white noise behavior; if $\alpha = 1.5$, the time series resemble Brownian motion, and if it is $0.5 < \alpha < 1.5$, there are positive correlations. If $\alpha \approx 1.0$ indicates a fractal-like behavior, if it reaches values above 1.0, the system tends to be less complex and linear [31].

Finally, to assess the regularity/irregularity of the RR time series, we also estimated the sample entropy (SampEn) calculated with m = 2 and r = 0.2, as described by Richman & Moorman [32].

Body composition estimation

Bioelectrical impedance analysis (BIA) is a non-invasive, low-cost, useful, and validated tool for estimating body composition [33]. The analysis is achieved by measuring the bioimpedance of an electrical current transmitted to the body through electrodes placed on the feet [34]. On the day of the study, a body composition analyzer, which employed BIA, was used to estimate body composition (BC-533 InnerScan Body Composition Monitor®, Tanita Corp., Itabashi-Ku Tokyo, Japan). Firstly, the heights of all subjects were measured and recorded. Then, participants were weighed, and body composition values were indirectly estimated using the device. The following body composition measures were collected for the BCS and Control groups: body fat percentage, body water percentage, muscle mass, bone mass, predicted daily calorie intake (DCI), metabolic age, and visceral fat rating (VFR). Particularly, VFR is given as a specific rating: (0–59 points). Ratings from 1 to 12 points indicate that the subject has a healthy level of visceral fat, while ratings from 13 to 59 points indicate that the subject has an excess level of visceral fat. The visceral fat rating has been widely applied in medical research as an indirect visceral fat amount in females [35] and mixed-gender groups [36]. We calculated the normalized visceral fat rating (nVFR) by dividing the visceral fat rating by the bodyweight of each participant.

Ethical considerations

This study was approved by the Research Ethics Committee No. 1503 from the Regional General Hospital No. 251 of the Mexican Institute of Social Security (IMSS). The Federal Commission for Protection Against Health Risks (COFEPRIS) authorizes this committee (authorization no. 17 CI 15 104 037) and the National Research National Commission of Bioethics in Mexico (CONABIO, authorization no. 15 CEI 002 2017033). This protocol was registered under the code R-2019-1503-012. All volunteers in this study signed an Informed Consent Form when they agreed to participate, and all methods were performed in accordance with the relevant guidelines and regulations.

Statistical analysis

The statistical analysis was done with GraphPad Prism version 8.00 for Windows (GraphPad Software, La Jolla California USA). Descriptive results were presented as median (25th–75th percentile) for quantitative variables and frequency (percentage) for categorical variables. A Shapiro-Shapiro-Wilk test was used to assess the normality of distribution. However, the data did not appear to have a normal distribution. Thus, the continuous variables were compared using one-tailed Mann-Whitney's U tests, and categorical variables were evaluated by Fisher's exact test. Associations between body composition and HRV measures (BCS group) were evaluated by Spearman's correlation coefficient. For all tests, results of $p<0.05$ were considered significant.

Results

Of 80 invited BCS women, 20 women were unwilling to participate in the study; 32 women were excluded because they were under chemotherapy, radiotherapy, or medication. Finally, the data of 27 BCS women were analyzed. Thirty-one women without cancer conformed the Control group with similar characteristics to the BCS group. Table 1 shows their general clinical parameters; as it was expected, there were no significant differences between both groups ($p > 0.05$).

Table 1
General clinical characteristics of study population

	BCS n = 27	Control N = 31	Significance p
Age (years)	56 (46–62)	51 (43–56)	0.11
Height (cm)	152 (148–157)	155 (150–158)	0.38
Weight (kg)	65.0 (55.4–76.3)	67.3 (58.2–69.8)	0.83
BMI (kg/m^2)	27.5 (24.7–32.4)	27.4 (24.9–37.4)	0.39
Menarche (years)	12 (12–13)	13 (12–14)	0.48
Number of gestations	2 (1–3)	3 (2–4)	0.13
Time since initial diagnose of cancer (years)	3.8 (2.4–6.0)	-	-
Time since surgery (years)	3.7 (1.4–4.8)	-	-
Lumpectomy/Mastectomy	24(88.8)	-	-
Family history of cancer (Yes)	11(40.7)	8(25.8)	0.17
Family history of cancer (No)	16(59.3)	23(74.2)	
Smoking	0 (0)	0 (0)	

[a]Data as presented as median (25th, 75th percentiles) or numbers (%). Mann-Whitney U test (continuous variables) between Breast cancer survivors (BCS) and Control groups. Fisher's exact test for categorical variables

Table 2 exhibits the HRV linear and nonlinear indexes, several significant differences ($p < 0.05$) were found between the BCS and Control groups. RRa_{ve}: 729 (648–802) vs. 795 (713–852) ms ; RMSSD: 16.5 (8.9–27.0) vs. 19.7 (14.2–28.5) ms; SD1: 11.6 (6.3–19.0) vs. 13.9 (10.0–20.1) ms; SD1/SD2: 2.5 (2.1–3.3) vs. 2.2 (1.9–2.7), SampEn: 1.5 (1.3–1.8) vs. 1.7 (1.5–1.8), and α2 0.6 (0.3–0.6) vs. 0.5 (0.4–0.5), respectively. A trend level of significance ($p = 0.05$) was observed for the scaling exponent α_1: 1.3 (1.2–1.5) vs. 1.2 (1.1–1.4). Notably, the RR_{ave} followed by the poincaré indexes had lower p-values than other HRV indexes. A representative illustration of Poincaré plots is shown in Fig. 1. The plot visually reveals a higher density of points in the center of Fig. 1a (compressed ellipse, BCS) compared to Control (expanded ellipse, Fig. 1b).

Table 2
Comparison of linear and nonlinear heart rate variability (HRV) indexes between the Breast Cancer Survivors (BCS) and Control groups

	BCS n = 27	Control n = 31	Significance p
RR_{ave} (ms)	729 (648–802)	795 (713–852)	**0.01**
SDNN (ms)	25.5 (14.3–34.4)	25.5 (18.4–36.5)	0.21
RMSSD (ms)	16.5 (8.9–27.0)	19.7 (14.2–28.5)	**0.03**
pNN50 (%)	0.5 (0.0–5.6)	1.5 (0.0–7.7)	0.12
LFnu	80.9 (67.7–88.2)	79.3 (69.8–84.1)	0.21
HFnu	19.0 (11.7–31.9)	20.6 (15.8–30.1)	0.21
SD1 (ms)	11.6 (6.3–19.0)	13.9 (10.0–20.1)	**0.02**
SD2 (ms)	32.8 (18.8–46.1)	32.7 (23.9–48.2)	0.22
SD2/SD1	2.5 (2.1–3.3)	2.2 (1.9–2.7)	**0.02**
SampEn	1.5 (1.3–1.8)	1.7 (1.5–1.8)	**0.04**
α_1	1.3 (1.2–1.5)	1.2 (1.1–1.4)	0.05
α_2	0.6 (0.3–0.6)	0.5 (0.4–0.5)	**0.04**

Data are presented as median (25th, 75th percentiles). Mann-Whitney's U tests between BCS and Control groups.

Table 3 depicts all the body composition measures indirectly estimated by BIA. Interestingly, only one body composition measure showed statistical differences ($p < 0.05$) between the BCS and Control groups: nVFR: 0.12 (0.11–0.13) vs.0.10 (0.08–0.12) points/kg, respectively. Additionally, a trend level of significance ($p = 0.07$) was observed for the VFR: 9 (6–10) vs. 7 (6–9) points.

Table 3
Comparison of body composition measures between Breast Cancer Survivors (BCS) and Control groups.

	BCS n = 27	Control N = 31	Significance p
Body fat (%)	35.5 (29.8–40.4)	34.8 (29.0–39.1)	0.24
Water (%)	44.5 (41.9–47.3)	45.2 (42.5–48.4)	0.16
VFR (points)	9 (6–10)	7 (6–9)	0.07
nVFR (points/kg)	0.12 (0.11–0.13)	0.10 (0.08–0.12)	**< 0.01**
Muscle mass (kg)	39.6 (33.6–42.7)	40.3 (38.3–42.0)	0.18
Bone mass (kg)	2.1 (2.0–2.3)	2.2 (2.1–2.3)	0.13
DCI (kcal)	1990 (1819–2146)	2008 (1891–2119)	0.31
Metabolic age (years)	49 (34–50)	49 (32–50)	0.43
[a]Data as presented as median (2 th, 75th percentiles). Mann-Whitney's U tests between BCS and Control groups.			
VFR: visceral fat rating; nVFR: normalized visceral fat rating; DCI: daily caloric intake			

We explored associations between body composition measures and HRV indexes in BCS. Strong positive and negative associations were found only for nVFR. Table 4 depicts the correlations between nVFR and HRV variables in BCS. Notably, abdominal fat is linked with multiple autonomic and nonlinear features variables. Conversely, data showed no significant correlation with RRa_{ve} and SampEn.

Table 4
Spearman correlations between normalized visceral fat rating (nVFR) and linear and nonlinear HRV indices in breast cancer survivors (BCS)

RR_{ave}	SDNN	RMSSD	pNN50	LFnu	HFnu	SD1	SD2	SD2/SD1	SampEn	α_1	α_2
-0.23	-0.58	-0.57	-0.58	0.40	-0.41	-0.57	-0.58	0.43	-0.21	0.49	0.53
0.11	**< 0.001**	**< 0.001**	**< 0.001**	**0.01**	**0.01**	**< 0.001**	**< 0.001**	**0.02**	0.14	**< 0.01**	**< 0.01**
In every cell, the top row indicates the correlation coefficient, and the bottom row indicates the significance											

Discussion

This study suggests that women who are BCS manifest cardiac autonomic modifications and HRV patterns changes compared to women with no-cancer diagnosis. BCS were characterized by a reduction of average RR interval and cardiac parasympathetic activity, a modified balance between long- and short-term HRV, lower irregularity of RR time series, and distinct fractal-like behavior. Moreover, a higher amount of visceral fat is likely manifested in BSC compared to control women.

The RR_{ave} was the HRV index that showed the most significant change between both groups (p = 0.01). We found lower RR_{ave} values (associated with higher average heart rate) in BCS compared to controls. Generally, changes in

RR intervals have been reported in BCS women even 18 years after different adjutant treatments of early breast cancer [37]. Recent results indicate that elevated heart failure risks have been observed after treatment with anthracyclines and trastuzumab treatment [38]. We found a lower cardiac parasympathetic activity (as indicated by RMSSD) in BCS compared to Control group. Previous reports have demonstrated that lower levels of RMSSD are associated with higher levels of average fatigue in BCS women [39]. Additionally, the values of RMSSD have been negatively correlated to interleukin-6 (IL-6) and C-reactive protein in BCS [39].

Our results for SD1 agree with previous studies that documented a lower short-term variability in BCS compared to controls [13]. SD1 is considered an index of instantaneous recordings of beat-to-beat variability and also represents cardiac parasympathetic activity. In cancer survivors, evidence indicates that fatigue is associated with a maladaptive autonomic profile characterized by higher sympathetic and lower parasympathetic activity [40]. Thus, we speculate that a diminished parasympathetic activity may be reflected as a disrupted cholinergic anti-inflammatory pathway [41], resulting in higher inflammation in BCS. There are emerging findings on inflammatory cytokines role in the recurrence of breast cancer [42].

The global variability and diminished parasympathetic activity can be detected visually in the representative poincaré plots (Fig. 1). It depicts that the Control group showed a greater beat-to-beat dispersion (Fig. 1b) of the RR time series compared to the BCS group (Fig. 1a).

Analysis of the SD2/SD1 ratio offers information on the relationship between long- and short-term HRV. The present study showed a higher ratio in BCS women. A lower SD2/SD1 ratio may reflect a decrease in SD1, an increase in SD2, or both. In the present study, an increase in SD1 was greater than in SD2. Some authors have interpreted this index as follows: a lower ratio implies both a decreased vagal tone and increased sympathetic influence [43,44].

A lower irregularity (indicated by SampEn) and different fractal-like behavior of the short- and long- term RR time series (indicated by α_1 and α_2, respectively) was found in BCS compared to Control. Lower values of SampEn and α_1 have been associated with pro-inflammatory processes (e.g., experimental endotoxemia and neonatal sepsis) in preclinical and clinical studies [45,46].

Interestingly, only the nVFR was different between the BCS and cancer-free women. This result is in line with a previous study in a sample of Iranian women, indicating that most BCS are abdominally obese [5]. Another study also demonstrated a high incidence of abdominal obesity among BCS from Malaysia [47]. According to some studies, fat gain is most common for women who undergo menopause because of cancer therapy and is often accompanied by changes in body composition [48]. Relevant findings suggest that abdominal adiposity could adversely affect the sympathetic and parasympathetic function [49]. Other findings suggest that an excess of visceral fat is associated with sympathetic activation [50].

According to the consulted literature, no studies have been conducted for evaluating the associations between central adiposity and linear and nonlinear indexes of HRV in BCS. Interestingly, we observed a significant negative association between visceral adiposity measured by BIA and parasympathetic function at BCS. A recent study found that insulin resistance and central adiposity showed the greatest influence on cardiac autonomic modulation of obese persons, increasing the risk for cardiovascular disease [51]. Thus, we consider that a concomitant increase of visceral fat, among other factors, may contribute to cardiac autonomic modifications and changes in HRV patterns in women who are BCS.

The HRV and VFR are promising tools for evaluating the ANS and body composition in BCS, respectively. These low-cost, affordable, and non-invasive tools can be routinely monitored in BCS for a clinical assessment or control of exercise training. Exercise training has mainly shown increment muscle strength, endurance, flexibility, decreased body fat percentage, waist circumference, and visceral fat area in cancer survivors [52]. Alternative therapies such as massages [53] and mindfulness [54] lead to an immediate increase of HRV, reduce inflammation, and improve BCS mood with cancer-related fatigue.

Limitations

A small sample size limits this study; our findings and interpretation should be confirmed in further clinical explorations. Nonetheless, previous studies have confirmed that even with a small number of participants (N = 15), it is possible to detect significant differences of HRV in BCS [13]. Additionally, the beat-to-beat change seen in the RR time series is not only under ANS influence. Humoral factors and respiratory variation may also play a role. Given the study cross-sectional nature, it is unknown whether some of the observed differences had already been present before breast cancer treatment.

Conclusions

Women who are BCS exhibited changes in HRV compared to controls; it included: a) lower average RR intervals, b) lower parasympathetic cardiac activity (as indicated by RMSSD and SD1), a modified balance between long- and short-term HRV, and a lower irregularity of RR time series (indicated by SD2/SD1 and SampEn, respectively) and different fractal-like behavior (indicated by α_1 and α_2). Additionally, survivors may have an increase of visceral fat compared to control women. Thus, a concomitant increase of visceral fat, among other factors, may contribute to cardiac autonomic disturbances and changes in HRV patterns in BCS. The visceral fat and HRV may be useful biomarkers for monitoring breast cancer survivors' health and well-being.

Declarations

Conflict of interest

The authors have no financial relationships relevant to this article to disclose.

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References

1. World Health. WHO | Breast cancer. *WHO* https://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/ (2018).

2. PAHO/WHO. Breast Cancer. https://www.paho.org/hq/index.php?option=com_content&view=article&id=5041:2011-breast-cancer&Itemid=3639&lang=en (2020).
3. Buttros, D. D. A. B. *et al.* Risk of metabolic syndrome in postmenopausal breast cancer survivors. *Menopause* **20**, 448–54 (2013).
4. Hamood, R., Hamood, H., Merhasin, I. & Keinan-Boker, L. Diabetes after hormone therapy in breast cancer survivors: A case-cohort study. *J. Clin. Oncol.* (2018) doi:10.1200/JCO.2017.76.3524.
5. Mohammadi, S., Sulaiman, S., Koon, P. B., Amani, R. & Hosseini, S. M. Association of nutritional status with quality of life in breast cancer survivors. *Asian Pacific J. Cancer Prev.* (2013) doi:10.7314/APJCP.2013.14.12.7749.
6. Mehta, L. S. *et al.* Cardiovascular Disease and Breast Cancer: Where These Entities Intersect: A Scientific Statement From the American Heart Association. *Circulation* (2018) doi:10.1161/CIR.0000000000000556.
7. Deluche, E. *et al.* Impact of body composition on outcome in patients with early breast cancer. *Support. Care Cancer* (2018) doi:10.1007/s00520-017-3902-6.
8. Brown, J. C., Cespedes Feliciano, E. M. & Caan, B. J. The evolution of body composition in oncology-epidemiology, clinical trials, and the future of patient care: facts and numbers. *J. Cachexia. Sarcopenia Muscle* **9**, 1200–1208 (2018).
9. Liu, L.-N., Lin, Y.-C., Miaskowski, C., Chen, S.-C. & Chen, M.-L. Association between changes in body fat and disease progression after breast cancer surgery is moderated by menopausal status. *BMC Cancer* **17**, 863 (2017).
10. Lakoski, S. G., Jones, L. W., Krone, R. J., Stein, P. K. & Scott, J. M. Autonomic dysfunction in early breast cancer: Incidence, clinical importance, and underlying mechanisms. *American Heart Journal* (2015) doi:10.1016/j.ahj.2015.05.014.
11. De Couck, M. & Gidron, Y. Norms of vagal nerve activity, indexed by Heart Rate Variability, in cancer patients. *Cancer Epidemiol.* (2013) doi:10.1016/j.canep.2013.04.016.
12. Lucini, D. *et al.* Endocrine Adjuvant Therapy might Impair Cardiac Autonomic Regulation in Breast Cancer Survivors. *Cardiol. Cardiovasc. Med.* **03**, (2019).
13. Palma, M. R. *et al.* The relationship between post-operative time and cardiac autonomic modulation in breast cancer survivors. *Int. J. Cardiol.* (2016) doi:10.1016/j.ijcard.2016.09.053.
14. Vigo, C. *et al.* Evidence of altered autonomic cardiac regulation in breast cancer survivors. *J. Cancer Surviv.* **9**, 699–706 (2015).
15. Arab, C. *et al.* Heart rate variability measure in breast cancer patients and survivors: A systematic review. *Psychoneuroendocrinology* **68**, 57–68 (2016).
16. Caro-Morán, E. *et al.* Heart Rate Variability in Breast Cancer Survivors After the First Year of Treatments: A Case-Controlled Study. *Biol. Res. Nurs.* (2016) doi:10.1177/1099800414568100.
17. Buccelletti, F. *et al.* Linear and Nonlinear Heart Rate Variability Indexes in Clinical Practice. *Comput. Math. Methods Med.* **2012**, 1–5 (2012).
18. Tsai, C. H. *et al.* Usefulness of heart rhythm complexity in heart failure detection and diagnosis. in *Scientific Reports* (2020). doi:10.1038/s41598-020-71909-8.
19. León-Ariza, H. H., Botero-Rosas, D. A. & Zea-Robles, A. C. HEART RATE VARIABILITY AND BODY COMPOSITION AS VO2MAX DETERMINANTS. *Rev. Bras. Med. do Esporte* (2017) doi:10.1590/1517-869220172304152157.

20. Mostarda, C. *et al.* Short-term combined exercise training improves cardiorespiratory fitness and autonomic modulation in cancer patients receiving adjuvant therapy. *J. Exerc. Rehabil.* **13**, 599–607 (2017).
21. Borgo, M. V. *et al.* Effect of tamoxifen on the coronary vascular reactivity of spontaneously hypertensive female rats. *Brazilian J. Med. Biol. Res.* (2011) doi:10.1590/S0100-879X2011007500099.
22. Erdfelder, E., FAul, F., Buchner, A. & Lang, A. G. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behav. Res. Methods* (2009) doi:10.3758/BRM.41.4.1149.
23. Young, F. L. S. & Leicht, A. S. Short-term stability of resting heart rate variability: influence of position and gender. *Appl. Physiol. Nutr. Metab.* **36**, 210–218 (2011).
24. Echeverria, J. C., Ortiz, R., Ramirez, N., Medina, V. & Gonzalez, R. A reliable method for abdominal ECG signal processing. *Comput. Cardiol. 1998. Vol. 25 (Cat. No.98CH36292)* **25**, 0–3 (1998).
25. Wessel, N. *et al.* Nonlinear analysis of complex phenomena in cardiological data. *Herzschrittmachertherapie und Elektrophysiologie* **11**, 159–173 (2000).
26. Malik, M., Bigger, J., Camm, A., Kleiger, R. & Task Force. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur. Heart J.* **17**, 354–381 (1996).
27. Burr, R. L. Interpretation of normalized spectral heart rate variability indices in sleep research: A critical review. *Sleep* (2007) doi:10.1093/sleep/30.7.913.
28. Tarvainen, M. P., Niskanen, J.-P., Lipponen, J. A., Ranta-Aho, P. O. & Karjalainen, P. A. Kubios HRV - heart rate variability analysis software. *Comput. Methods Programs Biomed.* **113**, 210–220 (2014).
29. Guzik, P. *et al.* Correlations between the Poincaré plot and conventional heart rate variability parameters assessed during paced breathing. *J. Physiol. Sci.* (2007) doi:10.2170/physiolsci.RP005506.
30. Huikuri, H. V *et al.* Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation* **101**, 47–53 (2000).
31. Peng, C. K., Havlin, S., Stanley, H. E. & Goldberger, A. L. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos* **5**, 82–87 (1995).
32. Richman, J. S. & Moorman, J. R. Physiological time-series analysis using approximate entropy and sample entropy. *Am. J. Physiol. Heart Circ. Physiol.* **278**, H2039–H2049 (2000).
33. Guida, B. *et al.* Bioelectrical impedance analysis and age-related differences of body composition in the elderly. *Nutr. Metab. Cardiovasc. Dis.* **17**, 175–180 (2007).
34. Long, V., Short, M., Smith, S., Sénéchal, M. & Bouchard, D. R. Testing Bioimpedance to Estimate Body Fat Percentage across Different Hip and Waist Circumferences. *J. Sports Med.* **2019**, 1–5 (2019).
35. Fernandez-Garcia, J. C. *et al.* An increase in visceral fat is associated with a decrease in the taste and olfactory capacity. *PLoS One* **12**, e0171204 (2017).
36. Puri, A., Singh, V., Pandey, S., Singh, C. K. & Singh, S. R. K. Visceral fat rating is a useful indicator in risk assessment among coronary artery disease patients treated with aggressive lipid lowering therapy. *Clin. Epidemiol. Glob. Heal.* (2014) doi:10.1016/j.cegh.2013.11.002.
37. De Azambuja, E. *et al.* Cardiac assessment of early breast cancer patients 18 years after treatment with cyclophosphamide-, methotrexate-, fluorouracil- or epirubicin-based chemotherapy. *Eur. J. Cancer* (2015) doi:10.1016/j.ejca.2015.08.011.
38. Boekel, N. B. *et al.* Heart failure after treatment for breast cancer. *Eur. J. Heart Fail.* (2020) doi:10.1002/ejhf.1620.

39. Crosswell, A. D., Lockwood, K. G., Ganz, P. A. & Bower, J. E. Low heart rate variability and cancer-related fatigue in breast cancer survivors. *Psychoneuroendocrinology* (2014) doi:10.1016/j.psyneuen.2014.03.011.
40. Fagundes, C. P. *et al.* Sympathetic and parasympathetic activity in cancer-related fatigue: More evidence for a physiological substrate in cancer survivors. *Psychoneuroendocrinology* (2011) doi:10.1016/j.psyneuen.2011.02.005.
41. Huston, J. M. & Tracey, K. J. The pulse of inflammation: Heart rate variability, the cholinergic anti-inflammatory pathway and implications for therapy. *J. Intern. Med.* **269**, 45–53 (2011).
42. Ma, Y. *et al.* IL-6, IL-8 and TNF-α levels correlate with disease stage in breast cancer patients. *Adv. Clin. Exp. Med.* (2017) doi:10.17219/acem/62120.
43. Goit, R. K., Pant, B. N. & Shrewastwa, M. K. Moderate intensity exercise improves heart rate variability in obese adults with type 2 diabetes. *Indian Heart J.* (2018) doi:10.1016/j.ihj.2017.10.003.
44. Goit, R. K., Jha, S. K. & Pant, B. N. Alteration of cardiac autonomic function in patients with newly diagnosed epilepsy. *Physiol. Rep.* **4**, e12826 (2016).
45. Reyes-Lagos, J. J. *et al.* Exogenous oxytocin reduces signs of sickness behavior and modifies heart rate fluctuations of endotoxemic rats. *Physiol. Behav.* **165**, (2016).
46. Lake, D. E., Richman, J. S., Pamela Griffin, M. & Randall Moorman, J. Sample entropy analysis of neonatal heart rate variability. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* (2002) doi:10.1152/ajpregu.00069.2002.
47. Yaw, Y. H. *et al.* Weight changes and lifestyle behaviors in women after breast cancer diagnosis: A cross-sectional study. *BMC Public Health* (2011) doi:10.1186/1471-2458-11-309.
48. Gadéa, E., Thivat, E., Planchat, E., Morio, B. & Durando, X. Importance of metabolic changes induced by chemotherapy on prognosis of early-stage breast cancer patients: A review of potential mechanisms. *Obesity Reviews* (2012) doi:10.1111/j.1467-789X.2011.00957.x.
49. Windham, B. G. *et al.* The relationship between heart rate variability and adiposity differs for central and overall adiposity. *J. Obes.* (2012) doi:10.1155/2012/149516.
50. Hillebrand, S. *et al.* Body fat, especially visceral fat, is associated with electrocardiographic measures of sympathetic activation. *Obesity* **22**, 1553–1559 (2014).
51. Oliveira, C. *et al.* Risk Factors Associated with Cardiac Autonomic Modulation in Obese Individuals. *J. Obes.* (2020) doi:10.1155/2020/7185249.
52. Kim, T. H. *et al.* Effects of exercise training on circulating levels of Dickkpof-1 and secreted frizzledrelated protein-1 in breast cancer survivors: A pilot single-blind randomized controlled trial. *PLoS One* (2017) doi:10.1371/journal.pone.0171771.
53. FERNÁNDEZ-LAO, C. *et al.* Attitudes towards massage modify effects of manual therapy in breast cancer survivors: a randomised clinical trial with crossover design. *Eur. J. Cancer Care (Engl).* **21**, 233–241 (2012).
54. Rådmark, Sidorchuk, Osika & Niemi. A Systematic Review and Meta-Analysis of the Impact of Mindfulness Based Interventions on Heart Rate Variability and Inflammatory Markers. *J. Clin. Med.* **8**, 1638 (2019).

Figures

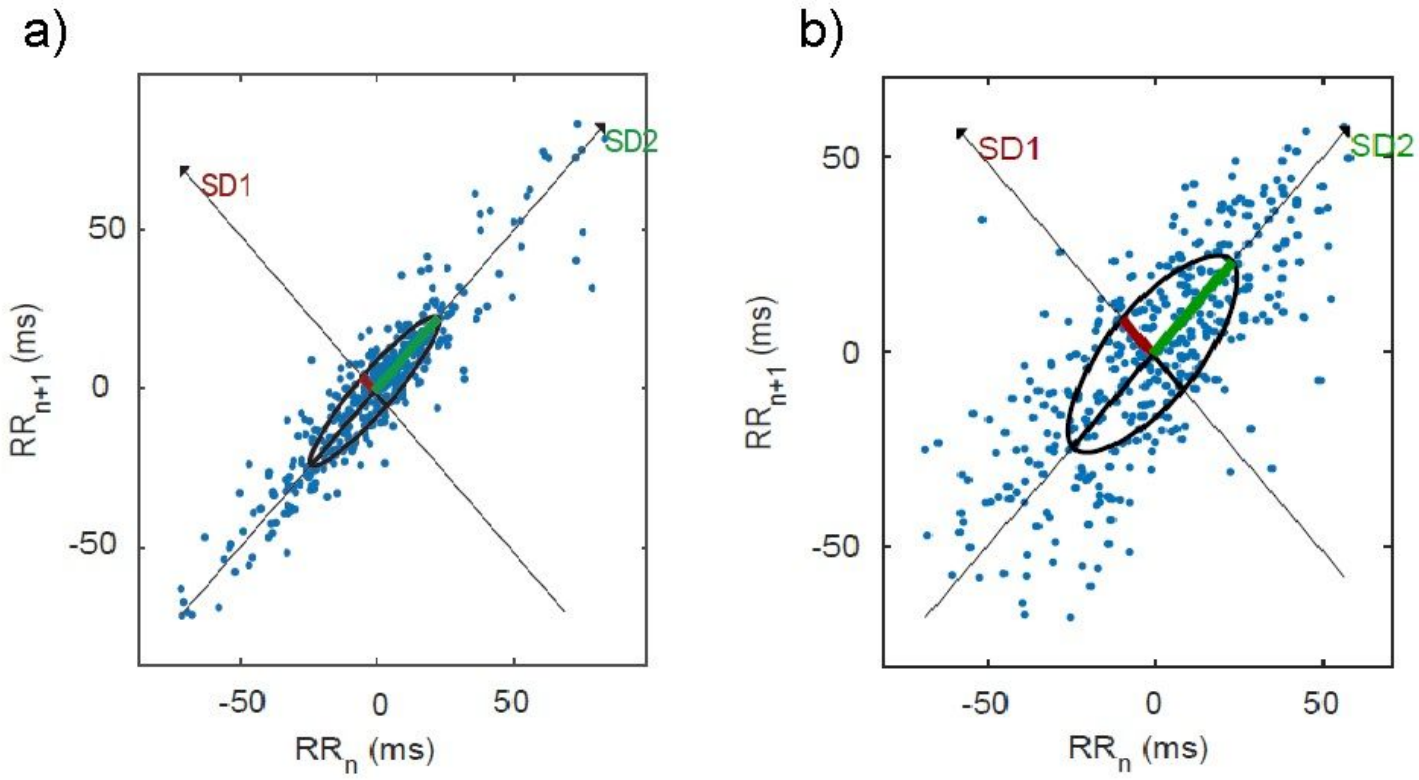

Figure 1

Representative patterns of Poincaré plots for: a) breast cancer survivor (BCS), SD1 =6.4 ms; SD2 =32.8 ms and SD2/SD1=5.12 and b) cancer-free women (Control), SD1=13.0 ms; SD2= 33.7 ms and SD2/SD1=2.60.