Factors Associated with Cardiorespiratory Fitness in Breast Cancer Survivors from the State of Santa Catarina, Brazil: Cross-Sectional Study

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Fatores Associados à Aptidão Cardiorrespiratória em Sobreviventes de Câncer de Mama do Estado de Santa Catarina, Brasil: Estudo Transversal

Factores Asociados con la Aptitud Cardiorrespiratoria en Sobrevivientes de Cáncer de Mama del Estado de Santa Catarina, Brasil: Estudio Transversal

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ABSTRACT

Introduction: Oxygen consumption (VO_2) is indicative of cardiorespiratory fitness (CRF) and lower levels are related to a higher risk of total mortality among individuals with cancer whose therapy can have adverse consequences on the cardiovascular system. **Objective**: To examine the associations of patient-reported sociodemographic, clinical, anthropometric outcomes and functional variables with CRF in 69 women (55±10 years) and to identify whether walking is a predictor of peak VO_2 variation in this population with breast cancer (BC). **Method**: Female BC survivors receiving hormone therapy after two types of surgery (breast-conserving and mastectomy) underwent a CRF test on a cycle ergometer to measure peak VO_2. A questionnaire containing sociodemographic, clinical data, patient reported outcomes (PROs) (depressive symptoms, sleep quality, fatigue, body image) and self-reported walking and tests to measure body fat percentage, waist circumference, flexibility and shoulder range of motion (RoM) were performed. **Results**: Unemployment and retirement were associated with low CRF, as was the use of aromatase inhibitors instead of tamoxifen. Depressive symptoms, worse body image, greater waist circumference, less flexibility and shoulder RoM were also associated with low CRF. Walking duration, controlled for age and body mass index (BMI), is a 13% predictor of peak VO_2 variance in this sample. **Conclusion**: These factors must be considered in understanding the CRF profile of BC survivors. As walking was a predictor of peak VO_2 variance, it should be recommended as a type of physical activity for patients with BC using hormone therapy.
Key words: breast neoplasms; exercise; walking; cardiorespiratory fitness; cancer survivors.

RESUMO

Introdução: O consumo de oxigênio (VO_2) é indicativo de aptidão cardiorrespiratória (ACR), e níveis mais baixos estão relacionados a um maior risco de mortalidade total entre indivíduos com câncer cuja terapia pode ter consequências adversas no sistema cardiovascular. **Objetivo:** Examinar as associações de desfechos sociodemográficos, clínicos, antropométricos relatados pelo paciente e variáveis funcionais com a ACR de 69 mulheres (55±10 anos), e identificar se a caminhada é um preditor de variação do pico de VO_2 nessa população com câncer de mama (CM). **Método**: Mulheres sobreviventes de CM recebendo terapia hormonal após dois tipos de cirurgias (conservadora e mastectomia) realizaram um teste de ACR em cicloergômetro para medir o VO_2 pico. Um questionário contendo dados sociodemográficos e clínicos; resultados relatados pelos pacientes (RRP) (sintomas depressivos, qualidade do sono, fadiga, imagem corporal); caminhada autorreferida; e testes para medir o percentual de gordura, circunferência da cintura, flexibilidade e amplitude do movimento ADM do ombro foram realizados. **Resultados**: Desemprego e aposentadoria foram associados à baixa ACR, assim como o uso de inibidores de aromatase ao invés de tamoxifeno. Sintomas depressivos, pior imagem corporal, maior circunferência da cintura, menor flexibilidade e ADM do ombro também foram associados à baixa ACR. A duração da caminhada, controlada por idade e índice de massa corporal (IMC), é um preditor de 13% da variância do VO_2 pico nesta amostra. **Conclusão:** Tais fatores devem ser considerados na compreensão do perfil de ACR de sobreviventes de CM. Como a caminhada foi um preditor da variância do VO_2 pico, deve ser recomendada atividade física para pacientes com CM em uso de hormonioterapia.
Palavras-chave: neoplasias da mama; exercício físico; caminhada; aptidão cardiorrespiratória; sobreviventes de câncer.

RESUMEN

Introducción: El consumo de oxígeno (VO_2) es indicativo de aptitud cardiorrespiratoria (ACR) y los niveles más bajos se relacionan con un mayor riesgo de mortalidad total entre las personas con cáncer cuya terapia puede tener consecuencias adversas sobre el sistema cardiovascular. **Objetivo**: Examinar las asociaciones de los resultados sociodemográficos, clínicos, antropométricos y variables funcionales informados por las pacientes con la ACR en 69 mujeres (55±10 años) e identificar si caminar es un predictor de la variación del VO_2 máximo en esta población con cáncer de mama (CM). **Método**: Mujeres sobrevivientes de CM que recibieron terapia hormonal después de dos tipos de cirugía (conservadora y mastectomía) se sometieron a una prueba de ACR en un cicloergómetro para medir el VO_2 máximo. Se aplicó un cuestionario que contenía datos sociodemográficos, clínicos, resultados informados por los pacientes (RIP) (síntomas depresivos, calidad del sueño, fatiga, imagen corporal) y caminata autoinformada y pruebas para medir el porcentaje de grasa corporal, la circunferencia de la cintura, la flexibilidad y el rango de movimiento (RoM) del hombro. **Resultados:** El desempleo y la jubilación se asociaron con una baja ACR, al igual que el uso de inhibidores de la aromatasa en lugar de tamoxifeno. Síntomas depresivos, peor imagen corporal, mayor perímetro de cintura, menor flexibilidad y RoM de los hombros también se asociaron con una baja ACR. La duración de la caminata, controlada por edad e índice de masa corporal (IMC), es un predictor del 13% de la variación del VO_2 pico en esta muestra. **Conclusión:** Estos factores deben ser considerados para comprender el perfil de ACR de los sobrevivientes de CM. Como la caminata fue un predictor de la variación del VO_2 pico, debe recomendarse actividad física para pacientes con CM en terapia hormonal.
Palabras clave: neoplasias de la mama; ejercicio físico; caminata; capacidad cardiovascular; supervivientes de cáncer.

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INTRODUCTION

Oxygen uptake (VO_2) is indicative of cardiorespiratory fitness (CRF) and lower levels are related to a higher risk of total cancer mortality among individuals with cancer[1]. Likewise, the peak power of incremental test is an indication of CRF, in which individuals with higher VO_2 tend to reach longer incremental test (i.e. higher intensity). Similarly, the improved CRF when maintaining a constant intensity will lead to a lower perceived exertion for the same absolute intensity after an intervention that improves CRF. Simultaneously, these methods can be used to assess CRF in different patients, including those with cancer[2].

Unfortunately, cancer therapy can have adverse consequences on the cardiovascular system[3]. Lower CRF in breast cancer (BC) survivors can lead to poorer health-related quality of life one-year after surgery[4], lower physical function[5], and higher mortality[6,7]. Studies conducted in Spain[8] and North America[3,7] have found that BC survivors have lower CRF compared to healthy women. A systematic review of 27 studies investigating CRF in BC survivors found that CRF was substantially lower in the post-adjuvant setting[9].

A recent systematic review on the determinants of CRF in healthy adults found that age, sex, socioeconomic status, anthropometric measures, vital parameters, biomarkers, physical activity (PA), smoking status and alcohol are related to CRF[10]. To date, two studies conducted in the USA have examined factors related to CRF in BC survivors. These studies found that higher age, elevated body mass index (BMI), disabilities of the arm, shoulder and hand, and not meeting PA guidelines are associated with worse CRF in this population[11,12].

The aim of this study was to examine the associations of sociodemographic, clinical, anthropometric, patient reported outcomes (PROs), and functional measures with CRF and to identify if walking is a predictor of variation in VO_2 peak in BC survivors, who underwent hormone therapy after two types of surgery.

METHOD

Cross-sectional study with baseline data from the MoveMama study, a randomized clinical trial registered at ClinicalTrials.gov (NCT03194997) and described in detail elsewhere[13].

Eligible participants were 18 years old BC survivors diagnosed with stage 0 to III of BC, who underwent one of two types of surgery (breast-conserving or mastectomy) from one to eight years ago and undergoing hormone therapy at the Oncology Research Center (CEPON) and residents of Santa Catarina, Brazil. Participants with major physical limitations, such as Parkinson's Disease or in wheelchair were excluded.

A questionnaire was administered by one of the two skilled investigators during an interview with each participant to collect sociodemographic and clinical factors. Patients were recruited through a list of hormone therapy users provided by the CEPON. The interviews were all previously scheduled and held on the premises of the Center for Health and Sports Sciences (CEFID), at the University of the State of Santa Catarina.

VO_2 was measured during a submaximal incremental test conducted with an electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands). During the test, the subjects breathed through a silicone face mask covering the mouth and nose, connected to an automated open circuit gas analysis system (Quark CPET; Cosmed Srl, Rome, Italy). The respiratory gas exchange was measured breath-by-breath. The incremental test started at 20 watts, with incremental increases of 15 watts every 3 minutes. The patients were encouraged to continue breathing for as long as possible until volitional exhaustion or until the heart rate (HR) reached 85% of the maximum HR, which was estimated by the equation 207 – 0,7* age. Peak power was defined as the power output attained at exhaustion or 85% of maximum HR. At the end of each stage of the incremental test, the rate of perceived exertion (RPE) was recorded using the Borg 6-20 category scale.

The VO_2 data were reduced to 15-second average values, and the last 15-second VO_2 value reached considered the VO_2 of each stage. The VO_2 peak was defined as the highest 15-second VO_2 value reached during the submaximal incremental test. An identical procedure was employed to determine the rest, each stage, and peak HR throughout the incremental test.

Waist circumference was measured with a tape (0 to 200 cm) with the participant in an orthostatic position. Fat percentage was estimated by the A-mode ultrasound technology (BodyMetrix™ BX2000; Intela Metrix® Inc., Livermore, CA, USA). The BodyMetrix is a portable device, operating by a linear probe at a frequency of 2.5-MHz associated with Body View™ Professional software[14]. All the measurements were made on the opposite side of the BC surgery (breast-conserving or mastectomy). The body fat percentage was estimated by Body Metrix software in accordance with modified "7-sites by Jackson & Pollock".

PROs were directly reported by the patients and evaluated by two investigators in a 30-minutes face-to-face interview. The outcomes listed below were measured with the respective questionnaires:

Depressive symptoms were investigated using the Beck Depression Inventory (BDI)[15]. Individual scores are

summed, and the scale has a maximum value of 63 points. Participants in the present study were categorized with absence of depression symptoms (scores from 0-10) and presence of depression symptoms (scores ≥ 11).

Sleep quality was investigated by the Pittsburgh Sleep Quality Index (PSQI)[16] consisting in seven subscales that are summed to reach a global PSQI score. A higher score indicates poorer sleep quality.

The 13-questions Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue)[17] measured fatigue, the total score ranges from zero to 52, higher scores mean less fatigue.

Body image was evaluated by the Body Image After BC Questionnaire (BIBCQ)[18,19]. BIBCQ is composed of 44 questions divided into six scales (vulnerability, body stigma, limitations, body concerns, transparency, and arm concerns). A higher score indicates a poorer perception of body image.

Flexibility was evaluated by the sit and reach bank test. Participants sat on the floor with knees straight and feet flat against the box. A ruler was fixed on top of the box from zero to 40 cm. The participants were asked to bend forward at the waist as far as possible while maintaining their legs straight. The best score of three trials was recorded.

Shoulder range of motion (RoM) was evaluated by the digital goniometer (Absolute Axis 360°), during flexion, abduction, and external rotation movements of each shoulder. The shoulder abduction movement was performed with the patient sitting, and the movements of shoulder flexion and external rotation with the patient lying on the stretcher.

Walking activity was measured by the short version of the International Physical Activity Questionnaire (IPAQ-short)[20]. IPAQ-short evaluates the frequency (times per week) and duration (minutes per week) that participants engaged in at least 10 continuous minutes of walking. For the purpose of this study, only data related to weekly minutes of walking were utilized since it is an accessible, cost-free and easy to practice activity.

To investigate the associations between sociodemographic and clinical factors and CRF characteristics (VO_2 peak, peak power and RPE) independent t tests (less than two groups) or one-way analysis of variance (ANOVA) and Bonferroni post hoc tests (more than two groups) were used. Multiple linear regression analysis was used to assess the relationship between the anthropometric, clinical, PROs and functional factors with VO_2 peak. In order to identify the walking contribution as a predictor in the variance of the outcome measured (VO_2 peak) a generalized linear model (GLM) was used. According to the literature[10-12] age and BMI are key potential predictors adopted in studies addressing CRF, therefore age was considered a confounder for the analysis of the association between anthropometric measures and CRF. All analyses were conducted in SPSS version 25.0 (SPSS Inc. Chicago, Illinois, USA).

Data collection took place at the College of Health and Sport Science of Santa Catarina State University in Brazil. The Institutional Review Board of UDESC approved the study (number 2,252,288) and the CEPON (number 2,319.138, CAAE: 67074017.6.3001.5355) too. All data collection was scheduled in advance with patients who agreed to participate in the study and had signed the Informed Consent Form.

RESULTS

Table 1 shows that women with one or more jobs had a higher VO_2 peak and achieved a higher peak power compared with retired or unemployed. For clinical factors, women receiving tamoxifen achieved higher peak power and presented higher RPE compared with those using AI.

Women who presented depressive symptoms had a decrease in VO_2 peak (95% CI: 4.3; 1.0) compared with women without depressive symptoms, as shown in Table 2. Body concerns (95% CI: 0.3; 0.1) and transparency (95% CI: 0.4; 0.0), subscales of body image, presented a negative relation with VO_2 peak. For anthropometric measures, for each ten-centimeter increase in waist circumference there was a decrease in VO_2 peak (95% CI: 0.1; 0.0). For functional measures, for each ten-centimeter increase in flexibility there was an increase in VO_2 peak (95% CI: 0.0; 0.1) and for each ten degrees increase in abduction of non-surgical side there was an increase in VO_2 peak (95% CI: 0.0; 0.1).

In this sample of BC survivors, 13% of the variance in VO_2 peak could be explained by the alteration in age and walking activity, as shown in Table 3. For each one-year increase in age there was a decrease in VO_2 peak of 0.09 $ml.kg^{-1}.min^{-1}$ (95% CI: 0.18, 0.00) and for each ten-minute increase per week in walking activity there was an increase in VO_2 peak of 0.2 $ml.kg^{-1}.min^{-1}$ (95% CI: 0.00, 0.04).

DISCUSSION

Findings from this study may help to identify poor VO_2 profiles in BC survivors, and consequently higher risk of mortality. This information can enhance health professionals to tailor physical activity intervention in the oncology setting. Women who had one or more jobs showed greater CRF than those who were retired or unemployed. It is likely that women who were unable to

Table 1. Sociodemographic and clinical factors associated with CRF in a sample of 69 breast cancer survivors from the state of Santa Catarina, Brazil

	Total sample (%)	VO_2 peak (ml.kg-1.min-1)	Peak power (watts)	RPE (Borg)
		p value	p value	p value
Occupational activity[a]		**0.019**	**0.012**	0.596
One or more jobs	33.3	21.1(4.1) A	68.3(14.1) A	14.5(3.5)
Retired or unemployed	53.6	18.3(3.0) B	53.4(20.3) B	15.2(2.3)
Domestic activities	13.0	19.1(2.1)	60.5(16.8)	14.4(3.9)
Economic level[a]		0.465	0.763	0.312
High income	2.9	18.2(0.2)	67.1(1.2)	12.0(1.4)
Middle income	29.0	18.5(3.1)	60.7(19.8)	15.3(3.3)
Low income	68.1	19.7(4.1)	58.4(19.2)	14.8(2.8)
Hormone therapy[b]		0.514	**0.001**	**0.049**
Aromatase inhibitors	52.5	19.2(4.5)	51.3(21.1)	14.0(2.8)
Tamoxifen	47.5	20.0(3.3)	67.2(15.0)	15.5(3.1)
Type of surgery[b]		0,708	0.582	0.062
Mastectomy	37.7	19.1(5.0)	60.9(17.3)	15.7(2.8)
Breast-conserving	62.3	19.4(3.3)	58.3(20.2)	14.3(2.9)
Nutritional status[b]		0.208	0.144	0.208
Overweight	60.9	18.8(3.5)	55.1(16.3)	14.9(2.6)
Normal	39.1	20.0(4.2)	62.0(20.3)	14.8(3.5)

Caption: RPE = Rating of perceived exertion.
([a]) Anova One-way test and Bonferroni post hoc.
([b]) Independent t test. Capital letters show the difference found with Bonferroni's post hoc test. A ≠ B.

work due to their BC diagnosis, surgery and treatment (chemotherapy, radiotherapy and hormone therapy) presented more side effects, such as physical impairments that lead to poor CRF. Another study in Brazil showed that women who returned to work after BC treatment were younger, with higher education, higher income, better psychological functioning and better physical profile in relation to disability and pain[21].

Women receiving AI presented worse CRF than women taking tamoxifen and were older (58.4 ± 9.2) than those taking tamoxifen (50.7 ± 9.2), some side effects as joint pain (arthralgia)[22] may occur. Studies investigating differences in the use of AI vs. tamoxifen have shown a higher risk of cardiovascular events in users of AI[23,24]. The use of AI may cause a decrease in the practice of PA for older women with BC[25], and it is known that its use can lead to musculoskeletal symptoms[26], osteoporosis and bone fractures[27]. Given the above, it is important that older women who receive AI are prescribed tailored exercises within the oncology setting.

The presence of depressive symptoms was found in 45% of the sample. An association among depressive symptoms and CRF was detected in other study with healthy populations[28], and to date, no other study investigating this association in BC survivors was found. It is possible that women with depressive symptoms are more likely to be inactive and have a poorer social life[29] which can lead to poorer CRF. Body image was also associated with VO_2 peak. Depressive symptoms are related to body image[30,31], which may explain this finding. Body image is usually related to BMI in other populations, however, in women with BC, dissatisfaction with body image goes beyond BMI, as it is influenced by treatment and type of surgery[32], as indicated by a meta-analysis that demonstrated better body image for women undergoing breast-conserving surgery when compared to those undergoing mastectomy[33].

The study findings demonstrate an association between VO_2 peak and waist circumference adjusted for age. Elevated BMI has been associated with an increased risk of cardiovascular disease and cancer recurrence in BC survivors[11]. Most of the sample were overweight (61%), and the women receiving hormone therapy are at risk of cardiovascular disease and should therefore be a priority for PA interventions. Also, flexibility and RoM of abduction on the non-surgical side was associated

Table 2. Patient reported outcomes, anthropometric measures and functional measures related with VO_2 peak in a sample of 69 breast cancer survivors from the state of Santa Catarina, Brazil

		Multivariate linear regression	
	Total sample	**Beta (CI 95%)**	**p-value**
PROs			
Presence of depressive symptoms	44.9%	-2.693(-4.382 to -1.004)	**0.002**
Sleep quality	7.2(4.3)	-0.174(-0.388 to 0.040)	0.109
Fatigue	38.5(9.0)	0.082(-0.015 to 0.1801)	0.095
Body image			
Vulnerability	18.7(8.2)	-0.063(-0.178 to 0.052)	0.279
Body stigma	31.8(10.4)	-0.025(-0.115 to 0.066)	0.589
Limitations	14.1(5.3)	-0.140(-0.309 to 0.029)	0.103
Body concerns	16.9(6.6)	-0.212(-0.342 to -0.082)	**0.002**
Transparency	11.0(4.2)	-0.263(-0.467 to -0.058)	**0.013**
Arm concerns	6.7(3.0)	-0.155(-0.464 to 0.153)	0.318
Anthropometric measures			
Fat percentage[a]	36.1(4.1)	-0.159(-0.398 to 0.079)	0.187
Waist circumference	90.6(12.5)	-0.078(-0.184 to 0.000)	**0.037**
Functional measures			
Flexibility	21.2(10.6)	0.098(0.017 to 0.180)	**0.019**
Shoulder RoM			
Surgical side			
Abduction	148.4(27.4)	0.012(-0.021 to 0.045)	0.460
Flexion	146.3(28.6)	0.024(-0.006 to 0.055)	0.116
External rotation	74.7(22.3)	0.016(-0.023 to 0.056)	0.409
Non-surgical side			
Abduction	155.3(25.3)	0.040(0.006 to 0.074)	**0.021**
Flexion	149.4(26.0)	0.024(-0.010 to 0.057)	0.165
External rotation	80.2(19.6)	0.012(-0.033 to 0.057)	0.594

Captions: CI = confidence interval; Beta = unstandardized B; PROs = patient reported outcomes; RoM = range of motion.
([a]) n = 61.
Note: Analysis controlled by age and BMI. For anthropometric measures, the analysis was controlled only by age.

Table 3. Generalized linear model of predictors variables in the variance of VO_2 peak in a sample of 69 breast cancer survivors from the state of Santa Catarina, Brazil

Variables included in the model	**B (CI 95%)**	**p-value**	**Overall effect**
			$X^2 = 12.924$ p = 0.005
Intercept (constant)	27.999 (22.022 to 33.977)	**<0.001**	
Age	-0.095 (-0.180 to -0.009)	**0.030**	
BMI	-0.159 (-0.319 to 0.001)	0.051	
Walking activity	0.021 (0.002 to 0.040)	**0.034**	

Captions: CI = confidence interval; BMI = body mass index.

with VO_2 peak. Women with better flexibility and greater shoulder RoM may have better independent daily activity[33], and, consequently, be more active, which can lead to a higher VO_2 peak.

After adjusting for age and BMI, walking was a predictor of variation in VO_2 peak in the study sample. The influence of age and BMI on VO_2 peak was demonstrated previously[11,12]. The aging process is

a natural predictor of CRF in a healthy population[34], and in BC survivors, aggressive treatments can cause some side effects that influence CRF in addition to the consequences from body changes[11,35]. However, despite the importance of PA, BC survivors do not reach the recommendations of 150 minutes of moderate activity per week plus two sessions of resistance exercises[36]. It is known that health care professionals in the oncology setting have an important role in providing information and improving the practice of PA in BC survivors[35]. As walking appears to be associated with the VO_2 peak, and is an easy, low-cost activity, or even an option of transport, interventions aiming to increase walking will likely be beneficial for BC survivors.

The limitations include the choice of a submaximal test to verify the VO_2 peak. Factors like smoking, alcohol use, diet, and time since diagnosis were not analyzed, which most likely restricted the ability to identify the predictors of VO_2 peak variation, as individuals with better CRF may present a healthy behavior. The walking activity was measured by a self-report instrument and may be a limitation because it is a subjective measurement and can overestimate the data.

CONCLUSION

Women who are unemployed or on medical leave, who were receiving AI, with depressive symptoms, worse scores of body image, larger waist circumference, lower flexibility, and lower RoM should be the priority regarding their CRF; healthcare providers should tailor their PA intervention considering these factors. Also, walking can be recommended as a type of PA for BC survivors, as it was considered a predictor of VO_2 peak variance in this study.

CONTRIBUTIONS

Leonessa Boing contributed to the study conception, methodology, analysis, wording, review and administration of the project; João Antônio Gesser Raimundo, Gustavo Soares Pereira, Melissa de Carvalho Souza Vieira, Alice Erwing Leitão, Tatiana de Bem Fretta, Juliana da Silveira Adriana, Patrícia Severo dos Santos Saraiva, Danielly Yani Fausto, Julia Beatriz Bocchi Martins contributed to the methodology, analysis, wording, review and editing; Brigid M. Lynch contributed to the wording, review and editing; Adriana Coutinho de Azevedo Guimarães contributed to the study concept, wording, review and editing, supervision and administration of the project.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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