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ORIGINAL ARTICLE

Cardiorespiratory fitness predicts cardiovascular health in breast cancer survivors, independent of body composition, age and time post-treatment completion

Lynnette M. Jones[1] · Lee Stoner[2] · Casey Brown[1] · J. Chris Baldi[3] · Blair McLaren[4]

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Abstract

Background Breast cancer treatment may increase non-cancer related mortality risk due to unintended cardiovascular consequences. The aim of this study was to investigate the strongest correlate of cardiovascular health (CVH) in female breast cancer survivors, cardiorespiratory fitness or fatness.

Methods Fifty-one women (59 ± 9 years, BMI 26.4 ± 4.8 kg/m^2) previously diagnosed and treated for primary breast cancer were assessed using pulse wave analysis to determine central arterial wave reflection (augmentation index, AIx) and central systolic blood pressure (cSBP). A composite *Z* score calculated which incorporated central double product and AIx, as an indicator of CVH. Dual energy X-ray absorptiometry was used to obtain total body fat percentage (BF%). Cardiorespiratory fitness was determined using the single-stage walk test to predict maximal oxygen uptake (VO_{2max}).

Results Linear regression analysis revealed that fitness was associated with AIx after adjusting for BF %, age and time post-treatment completion ($\beta = -0.271$, $p = 0.010$). A significant association between BF% and AIx after adjusting for fitness and age was found ($\beta = 0.166$, $p = 0.0005$); however, this association was lost when time post-treatment was included in the model ($\beta = 0.166$, $p = 0.167$). Both fitness ($\beta = -0.347$, $p = 0.0005$) and BF% ($\beta = 0.333$, $p = 0.013$) were independently associated with CVH in the fully adjusted model.

Conclusions This study provides evidence for an association between cardiorespiratory fitness and cardiovascular health in female breast cancer survivors. While fatness may be associated with cardiovascular health, it appears to be more strongly associated with age.

Keywords Breast cancer · Cardiovascular disease · Augmentation index · Double product · Body composition

Introduction

As the 5-year survival rate for women diagnosed with breast cancer continues to improve, the long-term health consequences of anti-cancer treatments are becoming apparent. Of particular concern is the disproportionate number of women with breast cancer who are susceptible to cardiovascular diseases (CVD) [1]. Death due to CVD rather than cancer is more likely in older breast cancer survivors [2] and those diagnosed with early stage disease [3]. Exposure to chemo- and radiation therapies, which alter normal functioning of the myocardium and vascular system increase this risk [4]. These effects appear to be exacerbated in older cancer survivors [5]. In addition, direct consequences include negative changes to body composition and cardiorespiratory fitness (CRF), which are unlikely to be monitored once treatment has been completed [6]. Given that peak mortality due to circulatory system disorders in breast cancer survivors appears at approximately 5 years post diagnosis and the incidence of cardiac dysfunction increases at 10–15 years post treatment completion, identification of potential predictors of

✉ Lynnette M. Jones
lynnette.jones@otago.ac.nz

1 School of Physical Education, Sport and Exercise Sciences, University of Otago, PO Box 56, Dunedin, New Zealand

2 Department of Exercise and Sport Science, University of North Carolina, Chapel Hill 27599, USA

3 Department of Medicine, University of Otago, Dunedin, New Zealand

4 Southern Blood and Cancer Service, Dunedin Hospital, Dunedin, New Zealand

cardiovascular health (CVH) would be useful for post-therapy management [1].

The deleterious effects of cancer treatment on CRF and body composition have been well documented [7, 8]. Marked reductions in CRF have been observed in breast cancer survivors, particularly in the post-adjuvant setting [5], and are likely compounded by inadequate physical activity, both during and following treatment completion [9]. Low CRF is associated with higher cancer-related mortality [5] including increased risk of CVD-related mortality in this sector of the population [10]. In addition, increases in body weight are commonly reported in breast cancer survivors, with gains of between 2 and 6 kg common in women undergoing chemotherapy treatment [6]. Obesity pre-diagnosis and weight gain during and post-treatment have been associated with an increased risk for breast cancer-related and all-cause mortality [11].

An improved understanding of the relative importance of these risk factors to cardiovascular health (CVH) in breast cancer survivors could permit identification of potential biomarkers for managing CVD risk. Therefore, the aim of this study was to assess measures of CVH, CRF, and body composition between older (60–75 years) and younger (40–55 years) women. We also sought to identify the strongest correlate of CVH in this group of breast cancer survivors: CRF or body fatness, after controlling for age and years since active treatment completion.

Methods

This observational study is reported in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [12].

Participants

Women were recruited from the greater Dunedin, New Zealand (NZ) area using posters placed in local medical practices and advertisements placed in local newspapers. Participants who responded to an advertisement were screened for eligibility by the lead author (LJ). Women were eligible if they were aged 40–55 years or 60–75 years, had previously been treated with chemotherapy and/or radiation therapy for breast cancer, and had completed active treatment at least 2 months prior. Women who were currently taking anti-estrogen agents and/or the monoclonal antibody agent Trastuzumab (Herceptin™) were included. Exclusion criteria included: distant metastases, diagnosed unstable cardiovascular disease, diabetes mellitus, or surgery only for primary breast cancer. Written, informed consent for all participants was obtained. At the initial contact, information on cancer stage, type of treatment, time since active treatment (i.e., chemotherapy or radiation therapy) completion, hormonal therapy use and the presence of comorbidities and relevant prescription medications was also recorded. Physical activity was calculated as the summation of the time spent in self-reported recreational physical activities multiplied by the duration of each session. The study was carried out with the approval of the University of Otago Human Ethics Committee (13/023).

Experimental design

Each participant made two visits to the laboratory, one visit to assess overall CVH, and a second to assess body composition and CRF. Cardiovascular health was assessed using previously reported standardized conditions [13]. Briefly, all measurements were made by the same researcher in a dimly-lit, climate controlled room between the hours of 8 and 10 am. All participants were fasted, consuming only water, and refrained from caffeine and supplement intake that morning, and strenuous physical activity and alcohol for 24 h prior to assessment. Participants were asked to lie quietly in a supine position for 20 min before assessments were made.

Cardiovascular health

Cardiovascular health measures included peripheral systolic and diastolic blood pressure, mean arterial pressure, pulse pressure, heart rate, and central systolic blood pressure (cSBP) and arterial wave reflection (augmentation index, AIx%). Double product was calculated using the product of cSBP*heart rate and is used as an indicator of myocardial function. A composite Z score incorporating central double product and AIx was calculated and used as a more global indicator of CVH. All parameters were derived from pulse wave analysis (R7 Cardioscope II, PulseCor, Auckland, New Zealand), taken from the arm on the non-involved side of the body, in accordance with recommendations for taking blood pressures on patients with breast cancer (American Cancer Society). The R7 incorporates an oscillometric blood pressure module, which complies with the Association for the Advancement of Medical Instrumentation (AAMI SP10) requirements and receives an A/A rating from the British Hypertension Society evaluation protocol [14]. The R7 records brachial blood pressures (~40 s) and then one set of suprasystolic (~30 mmHg > systolic pressure) recordings for 10 s. The suprasystolic pulse waveform is then used to determine central blood pressures. Briefly, the central pressure waveform was derived in the time-domain from the relationship between the total oscillatory pressure in the aorta and the total oscillatory pressure under the occlusion cuff [14]. Only recordings with a high signal to noise ratio (> 3 dB) were accepted. The cDP was calculated as pulse rate multiplied by central systolic blood pressure. AIx% was calculated using the formula: AIx% = ($P3$–$P0$)/($P1$–$P0$), where P0 is pressure at the onset of the pulse (diastolic), $P1$ is peak pressure of the incident wave (systolic), $P3$ is peak pressure of the reflective wave. This index describes the relative height of the reflected pressure wave when compared with the incident waveform. The reflected pressure wave is dependent on the structure and function of the vascular system [15, 16], and AIx% is an independent predictor of cardiovascular risk and mortality [17]. Two measurements over a 5-min interval were taken. If AIx measurements varied by > 4% or blood pressures by > 5 mmHg a third measurement was taken and the two closest recordings were averaged [18, 19].

Anthropometry and body composition

Height, weight, and waist circumference (WC) were measured immediately prior to body composition scanning. Dual energy X-ray absorptiometry (DXA, Lunar Prodigy, Lunar Corporation, Madison, WI, USA) was performed by a trained technician to obtain measures of lean tissue mass, total fat mass, total body fat percentage (BF%), and trunk fat. BF% was identified as the primary variable of interest.

Cardiorespiratory Fitness

CRF (maximal oxygen uptake, VO_{2max}) was estimated using the Single-Stage Treadmill Walk Test [20]. The participant was fitted with a heart rate (HR) monitor (Polar FT1; Polar Electro, Kempele, Finland) and began walking at 0% gradient at a self-selected walking speed, between 3.2 and 7.2 km/h, that elicited a HR corresponding to 50–70% of their age predicted maximum (220-age) after 4 min of walking. After the initial 4 min, speed remained constant and the gradient increased to 5% for a further 4-min stage. Speed, HR and perceived exertion were recorded at the end of the test. The gradient was then reduced to 0% and the participant continued walking slowly to cool down. This test is well tolerated and has been routinely used by cancer survivors in our laboratory. VO_{2max} (ml/kg/min) was predicted using the equation = 15.1 + (13.55 × speed (kph)) − (0.327 × final HR (bpm)) − (0.163 × speed × age (years)) + (0.00504 × final HR × age) [20].

Sample Size

Sample size calculations were made using GPower 3.1. To detect a 2-tailed, small-moderate correlation of 0.40 (95% CI − 0.29, 0.29), and setting the type 1 error at 5% and Type II error at 20%, 46 subjects are required. This number was inflated by 10–50% to account for sources of uncertainty and the potential for missing data.

Statistics

Statistical analyses were performed using Statistical Package for Social Sciences version 22 (SPSS, Inc., Chicago, Illinois). The women were classified as either younger (40–55 years) or older (60–75 years), as well shorter (< 5 years) or longer (> 5 years) years since treatment. Age differences in demographic characteristics were examined using the $\chi 2$ test for categorical variables, independent t test for continuous variables with normal distribution, and the Mann–Whitney U test for continuous variables with non-normal distribution.

Linear regression analysis was used to determine the independent associations of CRF (VO_{2max}) and fatness (BF%) with each of the four cardiovascular health outcomes (cSBP, DP, AIx, composite). To account for the influence of confounding variables, multivariate regression analyses were performed using Gaussian family generalized estimating equations. Model 1 adjusting for grouping by age and Model 2 additionally adjusted for grouping by years since treatment. Standardized (Beta) and non-standardized (β) coefficients are presented for cSBP, DP, AIx, and only the standardized coefficient for the composite score. All regression models were assessed for normality by examination of the model residuals plotted against their normal scores.

Results

Participants

Sixty-two women were screened for eligibility, of which 51 were deemed eligible. The 11 women deemed ineligible fell outside the age criteria. Participant demographic, cancer and comorbidity characteristics are presented in Table 1. There was no missing data for any of the included women.

Demographics

Participant demographic, cancer and comorbidity characteristics are presented in Table 1. The majority of women in this study were of New Zealand European descent and had Stage I–III disease. Of the entire cohort, 59% received both chemotherapy and radiation therapy, with slightly more women in the older group receiving radiation only. The median period of time since active treatment ended for the entire group was almost six and a half years; however, the older group were almost 9-years post-treatment, compared with 4 years in the younger group. A greater number of younger women remained on hormonal treatment at the time of the study. Thirty-nine percent of our cohort had one or more comorbidities.

Table 1 Demographic, cancer and comorbidity characteristics for older and younger women

Variable	Total ($n=51$)	Older ($n=27$)	Younger ($n=24$)
Continuous variables	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	59.0 ± 9.3	66.5 ± 4.3	50.0 ± 3.9**
Height (cm)	162.0 ± 6.1	162.0 ± 5.8	162.5 ± 6.5
Weight (kg)	69.5 ± 13.7	71.0 ± 13.2	67.8 ± 14.3
Body Mass Index (kg/m^2)	26.4 ± 4.8	27.1 ± 4.2	25.7 ± 5.5
Waist (cm)	89.3 ± 13.4	92.7 ± 11.8	85.4 ± 14.4*
Years post treatment	6.4 ± 5.7	8.7 ± 6.5	3.9 ± 3.3**
Categorical variables	*n*	[*n* (%)]	[*n* (%)]
Ethnicity			
New Zealand European	40	21 (78)	19 (79)
Maori	2	1 (4)	1 (4)
Other	9	5 (18)	4 (17)
Menopausal status			
Postmenopausal	40	27 (85)	13 (72)
Pre/Menopausal	11	0 (15)	11 (28)
Cancer stage			
I	9	6 (22)	3 (13)
II	23	9 (33)	14 (58)
III	11	6 (22)	5 (21)
DCIS	2	2 (8)	0
Unknown	6	4 (15)	2 (8)
Treatment type			
Chemotherapy only	9	4 (15)	5 (21)
Radiation only	12	8 (30)	4 (17)
Chemotherapy and Radiation	30	15 (55)	15 (62)
Hormonal therapy			
Tamoxifen	8	0	8 (46)
Aromatase inhibitor	3	1 (7)	2 (12)
Tamoxifen then Aromatase inhibitor	4	1 (7)	3 (18)
Herceptin then Aromatase inhibitor	2	2 (14)	0
Herceptin then Tamoxifen	1	0	1 (6)
Finished Hormonal Therapy	14	11 (73)	3 (18)
Comorbidities			
Hypertension	12 (24)	9 (33)	3 (13)
Hyperlipidaemia	8 (16)	7 (26)	1 (4)
Hypothyroid	5 (8)	3 (11)	2 (8)
Drug Class (Comorbidities)			
ACE inhibitor	9 (45)	6 (40)	3 (60)
Beta-Blocker	1 (5)	1 (6)	0
Statin	8 (40)	7 (47)	1 (20)
Angiotensin-II antagonist	1 (5)	1 (6)	0
Calcium antagonist	1 (5)	1 (6)	0
Thyroid hormone	5 (8)	3 (11)	2 (40)

*$p=0.05$

**$p<0.01$

Cardiovascular health

Table 2 presents the body composition, cardiorespiratory fitness and cardiovascular health measures. Compared to the younger group and all measures of CVH, other than pulse rate, were significantly higher in the older group of women. As a percentage of total body mass, percent body fat trended towards significance, with the older group

Table 2 Body composition, fitness and cardiovascular health measures in the total group ($n=51$), and older ($n=27$) and younger ($n=24$) women

	Total Mean (SD)	Older Mean (SD)	Younger Mean (SD)	*p*	*ES*
Body composition					
Lean tissue (kg)	39.9 (5.2)	39.9 (5.7)	40.0 (4.7)	0.97	− 0.02
Fat (kg)	26.9 (10.1)	28.5 (8.5)	25.1 (11.5)	0.26	0.34
Fat (%)	37.7 (8.0)	39.6 (5.8)	35.5 (9.6)	0.07	0.53
Trunk fat (kg)	13.6 (6.3)	14.7 (5.4)	12.4 (7.1)	0.21	0.37
Cardiorespiratory health					
Physical activity (mins/week)	238 (158)	224 (152)	254 (166)	0.51	0.19
VO_{2max} (ml/min/kg)	29.3 (4.9)	26.6 (3.1)	32.4 (4.8)	0.0005	− 1.47
Peripheral cardiovascular					
Pulse rate (bpm)	62 (8)	63 (8)	61 (9)	0.48	0.24
Mean arterial pressure (mmHg)	87 (9)	91 (7)	84 (10)	0.005	0.82
Systolic pressure (mmHg)	117 (15)	124 (12)	110 (14)	0.001	1.08
Diastolic pressure (mmHg)	72 (7)	74 (6)	70 (8)	0.046	0.57
Pulse pressure (mmHg)	45 (9)	49 (9)	40 (7)	0.0005	1.13
Central cardiovascular					
Systolic pressure (mmHg)	113 (13)	118 (11)	107 (12)	0.001	0.96
Double product	7019 (1306)	7429 (1243)	6558 (1242)	0.0005	0.70
Augmentation index (%)	112 (44)	131 (47)	91 (27)	0.001	1.08

ES effect size, VO_{2max} maximal oxygen uptake

higher than the younger group. Despite reporting a similar amount of physical activity, estimated VO_{2max} was significantly lower in the older group.

Fitness versus fatness

Linear regression analysis (Table 3) revealed the VO_{2max} and body fat % were independently associated with cSBP, DP and the composite score, and these associations persisted in a multivariate model, which adjusted for age and years since treatment. Further, the standardized betas suggest that VO_{2max} and body fat% are similarly related to cSBP, DP and the composite score. However, only VO_{2max} was associated with AIx following multivariate adjustment.

Discussion

The key finding from this study was that, after adjusting for age, CRF and body fatness were independently associated with AIx; however, only the association with fitness remained following inclusion of time since treatment was completed. CRF, independent of age and years since treatment may be a key factor in CVH in breast cancer survivors, while body fatness is more strongly associated with age.

Limitations and strengths

While our findings are internally robust, this study had potential limitations which should be addressed to contextualize the discussion which follows. First, the women recruited in this study were all recruited from the Otago region in New Zealand. Subsequent investigation is warranted to determine whether the findings generalize to other populations. Second, the primary outcome of this study was an estimate of CVH, not a cardiovascular endpoint. Use of a cardiovascular endpoint would have necessitated a longitudinal study. The current study represents a necessary step prior to initiating larger longitudinal studies. Finally, longitudinal studies are warranted to help establish temporality and causality. Strengths of this study include use of established CVH risk factors [17], and body composition measurement using DXA. Additionally, this is the first known study of its kind, and the findings make an important contribution to this literature.

Comparison to the literature

In the general adult population, low cardiorespiratory is inversely associated with CVD, and high body fat is positively associated with CVD [21, 22]. Further, it has been reported that high CRF may beneficially moderate the relationship between high fatness and CVD risk [22], supporting the American Heart Association's (AHA) policy statement calling for cardiorespiratory fitness as a vital sign [23]. We

Table 3 Linear association between measures of cardiovascular health with fatness (body fat %) and fitness (VO_{2max})

	Univariate					Multivariate									
						Model 1 (age adjusted)					Model 2 (multivariate adjusted)				
	β	Beta	LCI	UCI	p	β	Beta	LCI	UCI	p	β	Beta	LCI	UCI	P
Central systolic blood pressure (mm Hg)															
VO_{2max} (ml/kg/min)	– 0.749	– 0.290	– 0.564	– 0.015	0.039	– 0.702	– 0.271	– 0.288	– 0.255	0.000	– 0.702	– 0.271	– 0.368	– 0.175	0.000
Body fat (%)	0.551	0.346	0.077	0.616	0.013	0.528	0.332	0.149	0.514	0.000	0.528	0.332	0.034	0.629	0.029
Double product															
VO_{2max} (ml/kg/min)	– 81.22	– 0.306	– 0.579	– 0.033	0.029	– 76.89	– 0.290	– 0.480	– 0.099	0.003	– 76.89	– 0.290	– 0.472	– 0.107	0.002
Body Fat (%)	51.53	0.315	0.043	0.588	0.024	48.95	0.299	0.248	0.351	0.000	48.95	0.299	0.176	0.423	0.000
Augmentation index (%)															
VO_{2max} (ml/kg/min)	– 2.486	– 0.280	– 0.556	– 0.004	0.047	– 2.406	– 0.271	– 0.416	– 0.126	0.000	– 2.406	– 0.271	– 0.477	– 0.065	0.010
Body fat (%)	0.990	0.181	– 0.101	0.463	0.203	0.909	0.166	0.136	0.197	0.000	0.909	0.166	– 0.070	0.402	0.167
Composite															
VO_{2max} (ml/kg/min)		– 0.366	– 0.633	– 0.098	0.008		– 0.347	– 0.360	– 0.335	0.000		– 0.347	– 0.373	– 0.321	0.000
Body Fat (%)		0.352	0.083	0.621	0.011		0.333	0.266	0.400	0.000		0.333	0.070	0.596	0.013

Model 1 adjusted for age; Model 2: adjusted for age and years since treatment

Beta standardized, β non-standardized, *LCI* 95% lower confidence interval, *UCI* 95% upper confidence interval, VO_{2max} maximal oxygen uptake are unaware of any previous research investigating the relative importance of CRF and body fatness to CVH in breast cancer survivors.

Previous reports indicate that marked reductions in CRF are still present up to 7 years post cancer treatment completion [5, 24], including impairments in pulmonary, cardiac, and vascular and skeletal muscle function. Regular exercise training across the cancer trajectory is emerging as a cardio-protective intervention to attenuate the long term effects of cancer treatment [25]. CRF declines with age [26] and an inverse correlation between age and predicted VO_{2max} was evident in the current study. However, linear regression models for this study found an independent association between CRF and CVH, which remained after adjusting for age and also when the time post-treatment completion was included. The average self-reported PA levels in the two groups of women in this study exceeded the recommended 150 min per week of moderate intensity exercise [27]; however, the standard deviations showed a wide range, with many women not meeting the recommended PA guidelines. While predicted VO_{2max} values were within 5% of age-specific values for active women without cancer [26], strategies to reduce age-related loss of CRF in breast cancer survivors need further investigation.

Consistent with findings from the current study, high body fat mass is common amongst women who have received cancer treatment [28]. Increased fat mass is associated with an increased risk for breast cancer-related and all-cause mortality in breast cancer survivors [29]. In addition, high body fat (> 35%) in breast cancer survivors is associated with increases in serum markers of inflammation and endothelial dysfunction, C-reactive protein and serum amyloid A protein; biomarkers which are associated with poor vascular health, such as increased arterial stiffness [30]. Minimization of weight gain and promotion of weight loss following cancer treatment may attenuate these adverse changes, thereby leading to improvements in cardiovascular health and reduced mortality risk [31]. From the current study, limiting body fat increases as survivors age is of particular importance.

While there was little difference between groups for the level of exposure to cardio-toxic drugs and time from treatment completion, the mean AIx% was higher in older women and at the upper limit of the age-specific normal range as set by the manufacturer (38–140%). These findings concur with evidence showing that cancer treatment-induced alterations to the cardiovascular system may become chronic over time [32], compounding the natural decline in CVH associated with aging. Decreased left ventricular function with aging may impair myocardial function (central double product, cDP) and increase arterial wave reflection (AIx%); AIx% may be further implicated by early wave reflection due to an impaired capacity of the arterial system to buffer wave propagation [33]. In turn, increased left ventricular end systolic volume, reduced ejection fraction, and increased aortic stiffness have been observed soon after administration of anthracycline therapy in cancer survivors [34]; however, symptoms of cardiac dysfunction typically do not appear until approximately 10 years after treatment completion [32]. While the participants in the current study did not report overt cardiac dysfunction, these women had, on average, completed active treatment only approximately 3-years prior to assessment. This study provides evidence upon which future research can be undertaken to determine how the effects of aging on CVH interact with breast cancer treatment, and the modifiable role of fatness and CRF.

Clinical perspectives

The cardio-toxic effects of breast cancer treatment have been well characterized [35], with risks for ischaemic heart disease and heart failure increasing over time [36]. Findings from the current study: (1) lend support to the need for routine assessment of CVH; and (2) suggest that CRF warrants further attention as a modifiable risk factor for CVD risk in breast cancer survivors.

While monitoring changes in peripheral blood pressures and body mass are simple assessments that can be undertaken in the physician's office, CVH changes have traditionally required technologies that are often invasive and/or expensive. Measures such as central blood pressures, cDP and AIx can be obtained unobtrusively and with relatively low expense using pulse wave analysis. These measures reflect the oxygen demands placed on the myocardium and the ability of the arterial system to buffer pulse wave propagation [13, 37]. On the basis of this research we propose that routine noninvasive measures of CVH be trialed in the primary health care setting [38].

While CRF may be important to maintain CVH in cancer survivors, it can only be of value if it is malleable to lifestyle or other treatments. In the general population it has been reported that ~ 70% of CRF is determined by genetics, with the remaining portion being driven by lifestyle factors, particularly physical activity [39]. However, this malleable portion of CRF is apparently important. At least in the general population, it has been shown that a one metabolic equivalent increase in CRF, or 3.5 mL/kg/min increase in VO_{2max}, equates to a 13% and 15% decrease in CVD and all-cause mortality, respectively [40]. Further investigation is warranted to support temporality and causality, determine generalizability, and ascertain the feasibility of implementing CRF as a vital sign in this population.

Conclusion

Findings from the current study suggest that cardiorespiratory fitness is associated with cardiovascular health in breast cancer survivors after adjusting for age and time post-treatment completion. Furthermore, the association of body fat percentage with cardiovascular health remains when age is controlled for though is lost when treatment completion time is included in the model. These findings may permit identification of useful clinical indicators for managing cardiovascular risk in breast cancer patients. Given these promising findings with respect to CRF, a further confirmatory prospective study is warranted to support temporality and causality, including investigation of the interaction between natural aging, breast cancer treatment and cardiovascular health.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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