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Serum 25-hydroxyvitamin D and cancer-related fatigue: associations and effects on depression, anxiety, functional capacity and health-related quality of Life in breast cancer survivors during adjuvant endocrine therapy

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Abstract

Background: The adjuvant treatment with Aromatase Inhibitor (AI) is considered standard of care for postmenopausal breast cancer (BC) women with hormone receptor-positive (HR+), however, it often causes adverse effects such as cancer-related fatigue (CRF). The high prevalence of vitamin D deficiency in postmenopausal women who start adjuvant AI supports the hypothesis that hypovitaminosis D would be one of the biological explanations for toxicity of AI. This study aimed to identify the relationship between 25-hydroxyvitamin D [25(OH)D] and CRF, and to analyze their associations and effects on depression, anxiety, functional disability, muscle/joint aches and HRQL.

Methods: This prospective study included 89 postmenopausal women diagnosed with HR+ early BC in adjuvant endocrine therapy with AI. Anthropometric and body composition assessments were performed, as well as dietary assessments by application of 24-h dietary recall, at three time points, totaling 24 months of follow-up. The women completed the Cervantes Scale (CS), Hospital Anxiety and Depression Scale (HADS) and Health Assessment Questionnaire (HAQ). The CRF was determined from the Functional Assessment of Chronic Illness Therapy-fatigue (FACIT-F). The serum 25(OH)D was determined by electrochemiluminescence, with cut-off point above 75 nmol/L adopted as sufficiency. Generalized Linear Model (GLzM) and Generalized Mixed Model (GMM) analysis were used.

Results: At baseline, 36% ($n=32$) of the women presented CRF and 39.3% ($n=35$) had 25(OH)D below 75 nmol/L. None of the women reached the Estimated Average Requirements (EAR) of vitamin D. The causality between 25(OH)D and CRF was not significant. Longitudinally, lower levels of 25(OH)D had a negative effect on anxiety ($p=0.020$), Menopause and Health ($p=0.033$) and Vasomotor scores ($p=0.007$). Also, the CRF had a negative effect on anxiety

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($p=0.028$); depression ($p=0.027$); functional disability ($p=0.022$); HRQL ($p=0.007$); Menopause and Health ($p=0.042$), Psychological ($p=0.008$) and Couple Relations ($p=0.008$) domains; and on Health ($p=0.019$) and Aging ($p=0.036$) subdomains. Vasomotor subdomain ($\beta=-2.279$, $p=0.045$) and muscle/joint aches ($\beta=-0.779$, $p=0.013$) were significant with CRF only at baseline.

Conclusions: This study found negative effect of body adiposity on CRF. Still, the clinical relevance of 25(OH)D and CRF is highlighted, especially that of CRF, considering the consistent impact on several adverse effects reported by BC survivors during adjuvant endocrine therapy.

Keywords: Fatigue, Vitamin D deficiency, Cancer survivors, Breast neoplasms, Aromatase Inhibitors, Health-related quality of life

Background

Recently, female breast cancer (BC) has become the leading cause of cancer incidence worldwide [1]. In 2020, more than 2.2 million new cases of BC were estimated worldwide, and this number is expected to increase by more than 40% by 2040 [1].

The Aromatase Inhibitors (AI) are one of the adjuvant treatment options for postmenopausal BC women with hormone receptor-positive (HR+) [2]. Their mechanism of action is the inhibition or inactivation of aromatase, significantly reducing the plasma levels of estrogen from its androgenic precursors [2]. However, estrogen is involved in numerous physiological processes and, although related to the proliferation of tumor cells in HR+BC, it is expected that the depletion of this hormone generates significant adverse effects [3]. In this sense, the use of AI has been associated with negative effects on the urogenital system, interfering with sexual functioning [4]; depression [5]; increased risk of fractures and osteoporosis [6], joint pain or stiffness and fatigue [7].

Vitamin D deficiency has also been associated with symptoms such as non-specific joint pain, chronic fatigue and depression [5]. A 25-hydroxyvitamin D [25(OH)D] level of 75 nmol/L or higher has been associated with improved muscle strength and muscle pain syndrome, decreased risk of falls and fractures, reduced cytokine synthesis and lymphocytic proliferation [5], better tooth attachment [5, 8], improved depression and wellbeing [8, 9], reduction in the risk of autoimmune diseases, type 2 diabetes [5, 10], cardiovascular diseases [5, 10, 11], infectious [10] and neoplastic [5, 8, 10]. Estrogen has a positive effect on the activity of the vitamin D receptor and 1-alpha hydroxylase, an enzyme that converts 25(OH)D into biologically active 1,25-dihydroxyvitamin D [12]. Due to this, it is believed that the reduction of this hormone could unmask a 25(OH)D subclinical deficiency [12], which could intensify adverse effects related to the use of AI.

Furthermore, the vitamin D is involved in the modulating several inflammatory and pain pathways [13], in neurological [14] and oxidative [15] processes, in addition to calcium homeostasis [13], among others, which makes it essential for overall health [13], which is why its deficiency is one of the possible biological justifications for toxicity of AI.

The multicenter, prospective, and randomized trial ($n=500$) identified that 41.2% ($n=206$) of women with early-stage BC prematurely discontinued the hormone therapy with AI, with 79.1% ($n=163$) due to the adverse effects. Of this percentage, the two main causes were musculoskeletal symptoms (73.6%, $n=120$) and fatigue or insomnia (11.0%, $n=18$) [16]. In addition to affecting treatment adherence, the adverse effects of adjuvant endocrine therapy greatly impact the health-related quality of life (HRQL) [3].

According to the National Comprehensive Cancer Network (NCCN), cancer-related fatigue (CRF) is "a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [17]. CRF causes many physical, psychosocial, and economic consequences [18], thus being a strong predictor of HRQL in BC survivors, even after treatment [17, 19]. CRF is often linked to reports of other symptoms such as pain, insomnia, cognitive dysfunction [19], depression and anxiety [19, 20].

There are several interventions that aim to reduce CRF, such as physical exercise [21], acupuncture [22], yoga [23], mindfulness-based interventions [24], psychological intervention [25], cognitive behavioral therapy [26], educational intervention [27], and vitamin D supplementation [28], among others, each with its own evidence and specific indication, considering the complex and multidimensional nature of this clinical condition [29].

Considering the above, the aim of this study was to identify the relationship between 25(OH)D and CRF, as well as to analyze their associations and effects on depression, anxiety, functional disability, muscle/joint aches, and HRQL in BC survivors during adjuvant endocrine therapy. We hypothesized that those women with

lower 25(OH)D concentration and CRF, would have higher scores for both anxiety and depression, higher functional disability, worse HQRL and higher reports of muscle/joint aches. Also, we hypothesized that women with a worse nutritional status would have a worse score for CRF. To the best of our knowledge, this is the first prospective study to assess both the association and the effect of vitamin D and CRF on several aspects related to the health of BC survivors using AI.

Methods

Ethics statement, Study design and eligibility criteria

The study was approved by the Human Research Ethics Committee (nº. 1.331.949/15, addendum nº. 2.905.835/18) and conducted in accordance with the Declaration of Helsinki. A written free and informed consent was obtained from all participants.

From January 2016 to August 2018, postmenopausal women diagnosed with HR + early BC in adjuvant endocrine therapy with AI were consecutively recruited through the convenience non-probability sampling.

This prospective study was carried out at the Clinical Hospital of the Federal University of Uberlandia, Minas Gerais, Brazil. The face-a-face assessments were performed by properly trained researchers, at three time points: T0, baseline; T1, intermediate follow-up period, 12 months after T0; and T2, final follow-up period, 24 months after T0, totaling 24 months of follow-up.

The volunteers were included at any stage of the AI treatment, considering the following inclusion criteria: women aged between 18 and 80 years, who were HR + early BC and who had the physical, verbal and cognitive ability needed to respond to the tools necessary for the study. Eligible participants were excluded if they had metastasis, recurrence or contralateral BC, previous history of other cancers, another cancer concomitant with BC, age ≥ 80 years, wheelchair or bedridden, admission to palliative care and inability to attend collection. The diagram reporting the number of women recruited and selected in this study can be seen in the publication of Mazzutti and colleagues [30].

The collection of clinical and sociodemographic data occurred through the analysis of medical records or interviews.

Anthropometric and Body composition measurement

The weight and height were obtained by a mechanical scale with 100 g sensitivity and a vertical stadiometer with a 1 mm precision scale, respectively. Regarding the waist circumference (WC) and hip circumference, a flexible and inelastic tape was used. All measures were carried according to the specific protocol [31].

To assess the risk of metabolic complications, we adopted the cut-off ≥ 80 cm for WC and > 0.85 for the waist-to-hip ratio (WHR) [32]. Additionally, to assess abdominal fat, we calculated the waist-to-height ratio (WHtR), which cut-off is ≥ 0.5 as indicator of excess abdominal fat [33], and the conicity index, which estimation consider weight, height and WC [34].

The body mass index (BMI) was calculated in Kg/m^2 and the overweight was classified according to the age group: for the adult (age range 18—60 years), cut-off ≥ 25 kg/m^2 [32]; and elderly population (≥ 60 years), cut-off > 27 kg/m^2 [35].

The body composition was evaluated with horizontal tetra polar bioelectrical impedance analysis (BIA) (Biodynamics, model 450) according to the protocol [36, 37]. Considering the sensitivity of the exam to the presence of water body, we followed the recommended standardization of the method and the participants received pre-test guidelines in order to minimize measurement errors [36]. The body fat (BF) (in kilograms) was calculated by subtracting the fat free mass obtained using the predictive equation proposed by Kyle and collaborators [38] from the body weight and the percentage was obtained in relation to total body weight. The women whose exam detected water retention (total body water over 75%) were excluded from the BF analyses.

Dietary data

At each time point (T0, T1 and T2), three nonconsecutive 24-h dietary recall (24HR) were applied by nutritionists, totaling nine 24HR per participant. The 24HR, one referring to a weekend, were applied face-to-face (the first) and through telephone interviews, according to the methodology used in the Vigitel Study [39].

The quantification of nutrients from the 24HR was estimated through the Nutrition Data System for Research (NDSR) software, version 2010 (Minneapolis, MN, USA). The following nutrients were evaluated regarding the 25(OH)D concentration: vitamin D, calcium, total fat, total monounsaturated fatty acids (MUFA), total polyunsaturated fatty acids (PUFA), omega-3, omega-6, magnesium, zinc and fiber. The dietary intake of vitamin D was also evaluated in relation to Estimated Average Requirements (EAR). Furthermore, consumption of milk product, fish and seafood, and egg, in grams, were analyzed considering their relationship with 25(OH)D level.

Due to intra- and inter-individual variability of food consumption, the data were deattenuated [40] using the PC-Side software (Department of Statistics, Iowa State University, Ames, IA, USA), and were adjusted by residual method by the mean energy of the sample [41].

25-hydroxyvitamin D

Venous blood collection was performed at the hospital on a pre-scheduled date.

The serum 25(OH)D concentration was measured in nanomoles per liter (nmol/L) using electrochemiluminescence. The survivors were dichotomized into two subgroups using the cut-off points based on the guidelines from the Brazilian Society of Endocrinology and Metabolism (SBEM) and the Brazilian Society of Clinical Pathology/Laboratory Medicine (SBPC), with value equal to or greater ($\geq$) at 75 nmol/L (equivalent to 30 ng/mL) being considered sufficiency [42].

Patient-reported outcome (PRO) instruments

All participants replied by interview to the 31-item Cervantes Scale (CS-31), Functional Assessment of Chronic Illness Therapy-fatigue (FACIT-F), Hospital Anxiety and Depression Scale (HADS) and Health Assessment Questionnaire (HAQ).

CS-31. This is a HRQL questionnaire that considers particularities of the perimenopausal and postmenopausal women, having been developed in 2004 [43] and validated in Brazil in 2012 [44]. The CS-31 consists of 31 items rated on a Likert scale from 0 to 5 and divided into four domains, namely Menopause and Health (subdivided into Vasomotor Symptoms, Health and Aging), Sexuality, Couple Relations and Psychological, with scores range from 0 to 155 points. In cases of one or two unanswered questions, we used correction factors, but questionnaires with three or more unanswered questions were considered invalid [43]. In this study, the Cronbach's alpha were Global Score $\alpha = 0.89$, Menopause and Health $\alpha = 0.81$, Psychological $\alpha = 0.85$, Sexuality $\alpha = 0.84$, Couple Relations $\alpha = 0.75$, Vasomotor Symptoms subdomain $\alpha = 0.80$, Health subdomain $\alpha = 0.67$, and Aging subdomain $\alpha = 0.67$.

FACIT-F (version 4). This instrument of 40-item, validated in Brazil in 2010 [45], includes the 27-item Functional Assessment of Cancer Therapy-General (FACT-G) that assess the HRQL and 13 items that assess self-reported fatigue [46]. This scale measures four well-being subscales (physical, social/family, emotional and functional), one fatigue subscale (FACIT-Fatigue, score range 0–52), and derives to calculate the FACIT-F Trial Outcome Index (TOI) (score range 0–108), the FACT-G total score (score range 0–108) and the FACIT-F total score (score range 0–160). Items are rated on a Likert scale from 0 (not at all) to 4 (very much), with a higher score representing a better HRQL. The FACIT-Fatigue has a cut-off to identify presence of fatigue, with cut-off < 34 indicating clinically relevant fatigue [47]. In the present study, the Cronbach's alpha was FACIT-Fatigue $\alpha = 0.89$.

HADS. This self-reported questionnaire was developed in 1983 [48] and validated in Brazil in 1995 [49]. This scale comprising two subscales with seven items each, denominated HADS-A and HAD-D, which assessed anxiety and depression, respectively. Items are rated using a 4-point Likert scale with scores of 0 (minimally present) to 3 (maximally present), with higher scores indicating greater distress. The scores range from 0 to 21 and the following cut-off were adopted for both subscales: < 8 for non-cases, ≥ 8 for doubtful cases and ≥ 11 for the identification of cases [48]. In this study, the Cronbach's alpha were HADS-A $\alpha = 0.76$ and HADS-D $\alpha = 0.80$.

HAQ. This instrument assesses functional disability [50], consisting of 20 items that determine the capacity for various activities assessed in the week prior to the application of the questionnaire, such as dressing, getting up, walking, performing hygiene, reaching and holding objects, assessing movements of the upper and lower limbs and both simultaneously [51]. The items are subdivided into 8 categories and evaluated on a 4-point Likert scale, with scores range from 0 ("without difficulty") to 3 ("can't do it"), with higher scores representing greater disability [52]. This questionnaire was validated in Brazil in 1990 [53]. In this study, the HAQ presented Cronbach's alpha $\alpha = 0.88$.

Statistical analysis

The sample size was calculated considering a group of individuals and three measurements. Using the G*Power software, version 3.1 (Düsseldorf, Germany) [54], an F test was conducted using ANOVA repeated measures, based on an effect size f of 0.25, an alpha level of 0.05 and at 80% power, 28 women were required women at each study time. For cross-sectional analyses, the sample was 89 women, while for prospective analyses, the 38 women who participated at three time points of study were considered. All participants were coded by numbers at data collection and, remained this way in the database.

The sample was stratified by demographic and clinical characteristics.

Factors that interfere with 25(OH)D concentration were evaluated according to the established cut-off. For these analyses, we used Chi-Square Independence Test, Fisher Exact Test, Test-t Independent and Mann–Whitney.

We used Cronbach's alpha coefficient to assess the internal consistency of PRO Instruments, considering adequate values between 0.70 and 0.95 [55].

Generalized Linear Model (GLzM) and Generalized Mixed Model (GMM) analysis were used to verify, respectively, the associations and the effects (include effect of the time points and the interaction with the time points) of 25(OH)D concentration and FACIT-Fatigue

score (independent variables) on the PRO Instruments HADS-A, HADS-D, HAQ, CS-31 Global score, domains and subdomains, and on the CS-31 item – "Aching in muscle and/or joints" (dependent variables). Furthermore, GLzM and GMM were used to investigate causality in the association between 25(OH)D concentration and CRF.

The causality in the association between 25(OH)D concentration and FACIT-Fatigue score was also analyzed with Spearman's bivariate correlation. Correlation coefficients < 0.4 were considered weak correlations, between 0.4 and 0.6, moderate correlations, and > 0.6, strong correlations [56].

In addition, GLzM and GMM were used to verify the impact of anthropometric and body composition measurement (independent variables) on FACIT-Fatigue score (dependent variable).

All GLzM and GMM analysis included adjustment variables, as described in the respective tables. Regarding GMM, based on lowest Akaike Information Criterion (AIC) value, the best combination of the covariance matrices was AR1 (fixed effects) and variance components or AR1 (random effects). The adjustment method for multiple comparisons was Sidak.

We assessed the change in FACIT-Fatigue score between the three time points (T0, T1 and T2) considering a Minimum Clinically Important Difference (MCID) of 5% to classify the women between T0T1, T1T2, T0T2 and T0T1T2 into five clusters of CRF: The same, patients who maintained the FACIT-Fatigue score between T0T1, T1T2, T0T2 or who maintained the score at all three times (T0T1T2); Better, patients who improved the FACIT-Fatigue score between T0T1, T1T2, T0T2 or who improved at T1 and again at T2 (T0T1T2); Worse, patients who worsened the FACIT-Fatigue score between T0T1, T1T2, T0T2 or who worsened at T1 and again at T2 (T0T1T2); V, Patients who worsened the FACIT-Fatigue score at T1 and improved at T2 (T0T1T2); Inverted V, patients who improved the FACIT-Fatigue score at T1 and worsened at T2 (T0T1T2). The clusters in T0T1T2 were based on the classifications of each patient at T0T1 and again at T1T2.

The statistical analyzes were performed using IBM SPSS Statistics (Armonk, NY, USA), software package (SPSS Statistics for Windows, version 21.0), considering p-values < 0.05 statistically significant.

Results

In the present study, we evaluated the medical records of 256 patients using AI and 107 patients were excluded from the selection for the following reasons: metastasis ($n=35$), recurrence or contralateral BC ($n=20$), age ≥ 80 years ($n=23$), wheelchair or bedridden ($n=5$), admission to palliative care ($n=6$), previous history of other cancers (n = 5), another cancer concomitant with BC (n = 3), Alzheimer's disease ($n=3$), replacement with AI to tamoxifen ($n=2$), withdrawal from treatment ($n=1$), pulmonary edema ($n=1$), pulmonary hypertension ($n=1$), death ($n=1$) and *Sjoergren's* syndrome ($n=1$). The eligibility assessment of 149 patients resulted in 56 exclusions: refusal to participate ($n=22$), impossibility of telephone contact ($n=21$), not under treatment ≥ 6 months ($n=12$) and death ($n=1$). Four patients were excluded from the study due to recurrence of BC ($n=1$), incomplete questionnaires ($n=1$) and non-attendance of all appointments ($n=2$), totaling 89 women in the baseline (T0). For the prospective analyses, we considered the 38 women that participated at the three time points of the study, with the others having been excluded for the following causes: refusal to participate in the research ($n=16$), impossibility of telephone contact ($n=13$), end of treatment ($n=15$), inability to attend collection (problems with commuting) ($n=6$) and recurrence of BC ($n=1$).

The demographic and clinical characteristics of the 89 BC survivors were analyzed (Table 1).

Considering the overall, the medians (p25-p75) were 65 (58.5–69.5) years of age, 29.5 (18.1–41.8) months of time using AI, 4 (2–5) years of time diagnosis, and 16 (8–20) years of climacteric period. Regarding adjuvant endocrine therapy, 44.9% ($n=40$) of women used tamoxifen prior to starting AI (Table 1). At baseline, 36.0% ($n=32$) of women presented CRF and 39.3% ($n=35$) had serum 25(OH)D levels below 75 nmol/L (Data no shown).

Considering the FACIT-Fatigue subgroups, we identified that those women with CRF had a lower median of time using AI (23.3 months) even when compared to the subgroup without CRF (33.6 months) ($p=0.028$) (see Supplementary Table 1).

Among the factors that interfere with 25(OH)D concentration, we identified a significant difference regarding the season of the blood draw. In winter, the frequency of women with 25(OH)D concentration < 75 nmol/L was higher in relation to those with concentration ≥ 75 nmol/L ($p=0.039$). In addition, those women with 25(OH)D concentration < 75 nmol/L had a lower median of MUFA/PUFA ratio ($p=0.012$) and a higher median of omega-6 intake ($p=0.016$) even when compared to the subgroup ≥ 75 nmol/L (Table 2).

The dietary intake of vitamin D did not differ significantly between the 25(OH)D levels subgroups ($p=0.967$). However, it is important to note that none of the women reached the Estimated Average Requirements (EAR) of vitamin D (10 μg/day or 400 IU, [57]), at baseline or in the prospective phase. The mean and median (p25-p75) intake, 3.7 ± 1.7 μg/day and 3.5(2.3–5.0)μg/

Table 1 Demographic and clinical characteristics of the breast cancer survivors during endocrine therapy

Characteristics	Overall ($n=89$) n (%)
Age (years) – median (p25-p75)	65 (58.5–69.5)
< 60	25 (28.1)
≥ 60	64 (71.9)
Marital Status	
Single/ Divorced/Separated/Widow	50 (56.2)
Married	39 (43.8)
Partner	
No	22 (24.7)
Yes	67 (75.3)
Educational Level	
Below high school	61 (68.5)
High school or higher education	28 (31.5)
Income (minimum wage)	
< 3	53 (59.6)
≥ 3	36 (40.4)
Work activity	
Active	22 (24.7)
Inactive	67 (75.3)
Surgery	
Breast-conserving surgery	51 (57.3)
Mastectomy	38 (42.7)
Prior Radiotherapy	
No	14 (15.7)
Yes	75 (84.3)
Prior Chemotherapy	
No	21 (23.6)
Yes	68 (76.4)
Chemotherapy Regimen	
Adjuvant	53 (77.9)
Neoadjuvant	15 (22.1)
Prior Tamoxifen	
No	49 (55.1)
Yes	40 (44.9)
Tumoral Subtype	
Ductal	86 (96.6)
Lobular	3 (3.4)
Clinical Stage	
I	26 (29.2)
II	48 (53.9)
III	13 (14.6)
NR	2 (2.2)
Tumor Grade	
G1	14 (15.7)
G2	66 (74.2)
G3	5 (5.6)
NR	4 (4.5)
Molecular Subtype	
ER + and/or PR +, HER2- and Ki-67 < 14%	17 (19.1)
ER + and/or PR +, HER2- and Ki-67 ≥ 14%	37 (41.6)
ER + and/or PR +, HER2 +	29 (32.6)
NR	6 (6.7)
Months since start on AI	29.5 (18.1–41.8)
Years since diagnosis	4 (2—5)
Years since last menstrual period	16 (8—20)

Continuous variables are shown as median (p25-p75), and categorical variables are shown as absolute numbers and percentage frequency (in parentheses); Time point: T0, Baseline; Prior, before starting AI use; AI, aromatase inhibitor; *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor type 2 receptor, *Ki 67* Ki 67 antigen, -, negative; +, positive; *NR* Not reported, *G1* Well-differentiated tumor (low grade), *G2* Moderately differentiated tumor (intermediate grade), *G3* Poorly differentiated tumor (high grade). The Brazilian minimum wage was R$ 880.00

day, respectively, were low in the overall, including those women who used vitamin D supplementation (Table 2). Considering only the women who reported supplement use ($n=12$), the mean and median (p25-p75) intake of this nutrient were 4.5 ± 1.2 μg/day and 4.7 (3.5–5.7)μg/day, respectively (Data no shown).

Regarding the baseline, no significant association were found between 25(OH)D concentration and PRO Instruments. However, considering the longitudinal phase, we identified that low 25(OH)D level had negative effect on anxiety ($p=0.020$), Menopause and Health score ($p=0.033$) and Vasomotor score ($p=0.007$). The time of study had effect on anxiety ($p=0.018$) indicating that the women started endocrine therapy with more symptoms of anxiety, with an improvement over time. Still, the time of study had effect on Sexuality score (p = 0.036), with worse score in T2 compared to T1 (Table 3).

We investigated direct and reverse causality in the association between 25(OH)D concentration and CRF, but no significance was found in models effect tests. In longitudinal phase, the time of study had significant effect on 25(OH)D concentration, with lower level in T2 compared T1 ($p=0.045$), but only in model 1 with data adjusted for age (see Supplementary Table 2).

The causality was also investigated by bivariate correlation analysis, but without significance (r = -0.071, 95% [CI] = -0.310–0.160, $p=0.509$) (Data no shown).

Considering the clusters developed from the 5% MCID between the time points of study, we identified that the greater percentage of women was classified as "better", i.e. with improvement in FACIT-Fatigue score between T0T1 (57.9%, $n=22$), T1T2 (47.4%, $n=18$), T0T2 (55.3%, $n=21$) and T0T1T2 (36.8%, $n=14$) (Fig. 1).

Considering the multiple causes that may be involved in the development and, or in increasing CRF, we identified that there was no statistically significant difference between FACIT-Fatigue subgroups regarding age, race,

Table 2 Factors that interfere with 25-hydroxyvitamin D concentration in the breast cancer survivors during endocrine therapy

Factors	Overall ($n=89$)	25(OH)D		*p*
		< 75 nmol/L($n=35$)	≥ 75 nmol/L($n=54$)	
Age (years)	64.0 (7.7)	64.6 (7.6)	63.6 (7.8)	0.470 *
< 60	25 (28.1)	7 (28.0)	18 (72.0)	0.172θ
≥ 60	64 (71.9)	28 (43.8)	36 (56.3)	
Educational Level				
Below high school	61 (68.5)	26 (42.6)	35 (57.4)	0.347θ
High school or higher education	28 (31.5)	9 (32.1)	19 (67.9)	
Race Group				
White	83 (93.3)	33 (39.8)	50 (60.2)	1.000ʊ
Black	6 (6.7)	2 (33.3)	4 (66.7)	
Income (minimum wage)				
< 3	53 (59.6)	23 (43.4)	30 (56.6)	0.340θ
≥ 3	36 (40.4)	12 (33.3)	24 (66.7)	
Physical exercise				
No	53 (59.6)	22 (41.5)	31 (58.5)	0.262θ
Yes	36 (40.4)	13 (36.1)	23 (63.9)	
Current Smoking				
No	80 (89.9)	30 (37.5)	50 (62.5)	0.308θ
Yes	9 (10.1)	5 (55.6)	4 (44.4)	
Alcohol Intake				
No	66 (74.2)	29 (43.9)	37 (56.1)	0.131θ
Yes	23 (25.8)	6 (26.1)	17 (73.9)	
Supplementation				
No	75 (84.3)	29 (38.7)	46 (61.3)	0.193ʊ
Yes, vitamin D	3 (3.4)	0 (0.0)	3 (100.0)	
Yes, calcium	2 (2.2)	2 (100.0)	0 (0.0)	
Yes, both	9 (10.1)	4 (44.4)	5 (55.6)	
Season of the blood draw				
Summer	44 (49.4)	13 (29.5)	31 (70.5)	**0.039**θ
Autumn	30 (33.7)	12 (40.0)	18 (60.0)	
Winter	15 (16.9)	10 (66.7) [a]	5 (33.3) [b]	
Months since start on AI	29.5 (18.1–41.8)	25.5 (18.3 – 38.7)	30.0 (17.8 -48.1)	0.413 **
Daily Sun Exposure (minutes/day)	30 (15—60)	30 (10—60)	30 (18.8—60)	0.313 **
BMI (Kg/m^2)	28.3 (25.4–31.4)	28.7 (25.4–31.4)	28.0 (25.3–31.6)	0.804 **
Body Fat (Kg)	28.3 (24–34.9)	27.7 (24.8–36.2)	28.5 (23.9–34.3)	0.781 **
Body Fat (%)	40.2 (36.8–44.4)	40.2 (36.7–47.6)	40.9 (37.6–44.3)	0.904 **
Calcium Concentration (mg/dL)	9.4 (9.2–9.9)	9.4 (9.1–9.8)	9.5 (9.3–9.9)	0.173 **
Parathyroid Hormone Concentration (pg/mL)	44.0 (33.2–55.3)	43.0 (32.6–57.5)	44.9 (34.2–54.3)	0.886 **
Milk product intake (g)	112.1 (27.5–222.0)	123.3 (28.5–225.3)	96.04 (12.9–221.6)	0.491 **
No	10 (11.2)	2 (20.0)	8 (80.0)	0.304ʊ
Yes	79 (88.8)	33 (41.8)	46 (58.2)	
Fish and Seafood intake				
No	72 (80.9)	31 (43.1)	41 (56.9)	0.174θ
Yes	17 (19.1)	4 (23.5)	13 (76.5)	
Egg intake				
No	55 (61.8)	20 (36.4)	35 (63.6)	0.467θ
Yes	34 (38.2)	15 (44.1)	19 (55.9)	
Dietary Intake				
Vitamin D (μg)	3.5 (2.3–5.0)	3.5 (2.4–5.0)	3.5 (2.2–5.0)	0.967 **

Table 2 (continued)

Factors	Overall ($n=89$)	25(OH)D		*p*
		< 75 nmol/L($n=35$)	≥ 75 nmol/L($n=54$)	
Calcium (mg)	475.8 (375.1–586.7)	464.9 (377.5–558.8)	478.2 (371.1–591.9)	0.788 **
Total Fat (g)	47.8 (5.0)	47.0 (4.3)	48.4 (5.4)	0.196 *
MUFA (g)	16.4 (2.4)	15.8 (2.2)	16.8 (2.4)	0.478 *
PUFA (g)	12.0 (1.7)	12.2 (1.5)	11.9 (1.8)	0.052 *
MUFA/PUFA Ratio	1.4 (1.2–1.6)	1.3 (1.1–1.4)	1.4 (1.3–1.6)	**0.012** **
Omega-3 (g)	1.5 (1.4–1.6)	1.5 (1.4–1.6)	1.5 (1.4–1.6)	0.551 **
Omega-6 (g)	10.4 (1.5)	10.7 (1.2) [a]	10.2 (1.7) [b]	**0.016** *
n6/n3 fatty acids ratio	7.0 (6.5 – 7.4)	7.1 (6.9 – 7.4)	6.7 (6.3 – 7.5)	0.193 **
Magnesium (mg)	192.6 (173.6–216.4)	195.8 (176.1–221.4)	192.6 (172.8–207.7)	0.518 **
Zinc (mg)	8.7 (1.4)	8.8 (1.5)	8.6 (1.4)	0.534 *
Fiber (g)	15.7 (3.8)	16.5 (4.1)	15.1 (3.5)	0.113 *

Continuous variables are shown as mean (standard deviation) or median (p25-p75), and categorical variables are shown as absolute numbers and percentage frequency (in parentheses); Time point: T0, Baseline; 25(OH)D, 25-hydroxyvitamin D; AI, aromatase inhibitor; *BMI* Body Mass Index, *MUFA* Total Monounsaturated Fatty Acids, *PUFA* Total Polyunsaturated Fatty Acids, n6/n3 fatty acids ratio, estimated ratio of omega-6 to omega-3 fatty acids. The Brazilian minimum wage was R$ 880.00

[θ] Chi-Square Independence Test

[ϖ] Fisher Exact Test

[*] Test-t Independent

[**] Mann–Whitney. Different superscript letters represent statistical significance when comparing column proportions. Bold value is statistically significant at $p<0.05$

educational level, income and clinical stage (see Supplementary Table 1), and neither in relation to physical exercise ($p=0.980$) (Data no shown). Still, the dietary intake of vitamin D did not differ significantly between the women with CRF (3.8 ± 1.8 µg/day) and without CRF (3.7 ± 1.7 µg/day) ($p=1.000$) (Data no shown).

Moreover, we investigated the association of CRF with anthropometric and body composition parameters (Table 4), considering that these variables also may be related to CRF. At baseline, the women with lower FACIT-Fatigue score presented higher BMI (β = -0.637, CI = -0.986 to -0.287, $p<0.001$), WC (β = -0265, CI = -0.427 to -0.103, $p=0.001$), WHtR (β = -41.972, CI = -67.155 to -16.788, $p=0.001$) and body fat (Kg) (β = -0.285, CI = -0.526 to -0.045, $p=0.020$) (Table 4). In the longitudinal phase, the WC ($p=0.001$) and conicity index ($p=0.021$) had negative effect on CRF, and those women with a lower FACIT-Fatigue score presented WC > 80 cm and conicity index above the median (> 1.3) (Table 4). Considering the FACIT-Fatigue subgroups, we identified significant difference in relation the BMI ($p=0.002$), WC ($p=0.004$) and WHtR ($p=0.002$), with women with CRF presenting worse scores (Table 4).

At baseline, negative associations were observed between FACIT-Fatigue and PRO Instruments, indicating that the women with CRF presented more anxiety (β = -3.779, CI = -5.498 to -2.059, $p<0.001$), depression (β = -4.799, CI = -6.559 to -3.038, $p<0.001$), functional disability (β = -0.554, CI = -0.803 to -0.304, $p<0.001$) and muscle/joint aches (β = -0.779, CI = -1.394 to -0.165, $p=0.013$). Also, these women presented worse HRQL (β = -34.337, CI = -45.278 to -23.397, $p<0.001$) and worse score in the following domains and subdomains of the CS-31: Menopause and health (β = -17.143, CI = -22.882 to -11.405, $p<0.001$), Psychological (β = -16.214, CI = -20.792 to -11.636, $p<0.001$), Vasomotor (β = -2.279, CI = -4.509 to -0.050, $p=0.045$), Health (β = -6.325, CI = -8.513 to -4.138, $p<0.001$) and Aging (β = -8.539, CI = -11.777 to -5.301, $p<0.001$) (Table 5).

Longitudinally, the CRF had negative effect on Couple Relations domain ($p=0.008$), and the significances were maintained for anxiety ($p=0.028$), depression ($p=0.027$), functional disability ($p=0.022$), HRQL ($p=0.007$), Menopause and Health ($p=0.042$), Psychological ($p=0.008$), Health (p = 0.019) and Aging ($p=0.036$) (Table 5).

The time of study had effect on anxiety ($p=0.035$), with the significance indicating worse score in T0 compared T1 (Table 5). In addition, the interaction between FACIT-Fatigue and time points of study had effect on Psychological domain ($p=0.004$), with significance in the CRF subgroup, indicating a worse score in this domain in T0 compared T1 (Table 5).

Discussion

Our results showed that slightly more than one-third of the BC survivors had CRF and low serum 25(OH)D levels. The women with CRF had been using AI for a shorter time when compared to the subgroup without CRF. The

Table 3 Associations and effects of 25(OH)D on PRO Instruments in the baseline and in the longitudinal phase

PRO Instrument	Baseline ($n=89$)							Longitudinal phase[1] ($n=38$)					
	25(OH)D		β	95% CI		Wald Chi-square	*p	Time points		25(OH)D		Model Effects Test	
	< 75 nmol/L	≥ 75 nmol/L		Lower	Upper					< 75 nmol/L	≥ 75 nmol/L	Effects	Df	**p
HADS-A	7.95 ± 1.02	8.09 ± 0.97	-0.017	-0.244	0.211	0.021	0.886			8.34 ± 0.94[a]	6.69 ± 0.84[b]			
								T0	10.16 ± 1.20[a]	10.85 ± 1.35	9.48 ± 1.25	**Time points**	2	**0.018**
								T1	7.47 ± 0.91[b]	8.50 ± 1.18	6.45 ± 0.89	**25(OH)D**	1	**0.020**
								T2	4.90 ± 1.21[c]	5.67 ± 1.28	4.14 ± 1.31	**Interaction[2]**	2	0.822
HADS-D	6.32 ± 1.10	7.57 ± 1.02	-1.249	-3.170	0.672	1.623	0.203			7.12 ± 1.08	6.82 ± 0.97			
								T0	7.21 ± 1.36	7.05 ± 1.50	7.37 ± 1.42	**Time points**	2	0.950
								T1	6.88 ± 1.04	7.29 ± 1.38	6.47 ± 1.01	**25(OH)D**	1	0.692
								T2	6.81 ± 1.38	7.02 ± 1.45	6.61 ± 1.48	**Interaction[2]**	2	0.647
HAQ	0.96 ± 0.15	1.08 ± 0.14	-0.112	-0.374	0.150	0.699	0.403			0.92 ± 0.14	0.91 ± 0.12			
								T0	0.88 ± 0.17	0.90 ± 0.20	0.87 ± 0.18	**Time points**	2	0.693
								T1	0.95 ± 0.13	1.06 ± 0.17	0.84 ± 0.13	**25(OH)D**	1	0.946
								T2	0.91 ± 0.18	0.79 ± 0.19	1.02 ± 0.19	**Interaction[2]**	2	0.063
CS-31 Total Score	65.98 ± 6.85	74.20 ± 6.10	-8.219	-20.958	4.521	1.599	0.206			62.88 ± 8.25	54.62 ± 7.44			
								T0	61.89 ± 10.09	67.67 ± 11.32	56.11 ± 10.42	**Time points**	2	0.856
								T1	57.53 ± 7.83	59.87 ± 10.66	55.19 ± 7.69	**25(OH)D**	1	0.189
								T2	56.83 ± 10.41	61.10 ± 11.13	52.55 ± 11.26	**Interaction[2]**	2	0.800
CS-31 Menopause and Health Domain	36.26 ± 3.55	39.80 ± 3.15	-3.534	-10.126	3.059	1.104	0.293			32.88 ± 3.77[a]	26.47 ± 3.37[b]			
								T0	29.32 ± 4.61	31.53 ± 5.30	27.11 ± 4.73	**Time points**	2	0.747
								T1	30.72 ± 3.53	33.33 ± 4.78	28.12 ± 3.47	**25(OH)D**	1	**0.033**
								T2	28.99 ± 4.77	33.79 ± 5.17	24.19 ± 5.19	**Interaction[2]**	2	0.592
CS-31 Psychological Domain	13.78 ± 3.02	16.27 ± 2.69	-2.493	-8.113	3.127	0.756	0.385			11.78 ± 3.43	10.70 ± 2.95			
								T0	16.45 ± 4.07	17.44 ± 4.86	15.46 ± 4.14	**Time points**	2	0.217
								T1	10.62 ± 3.23	12.40 ± 4.82	8.85 ± 3.13	**25(OH)D**	1	0.715
								T2	6.64 ± 4.22	5.50 ± 4.69	7.79 ± 4.67	**Interaction[2]**	2	0.597
CS-31 Sexuality Domain	11.68 ± 1.48	13.20 ± 1.31	-1.520	-4.267	1.226	1.177	0.278			10.77 ± 1.89	13.02 ± 1.65			
								T0	10.91 ± 2.29[a,b]	10.42 ± 2.74	11.41 ± 2.32	**Time points**	2	**0.036**
								T1	10.02 ± 1.75[a]	7.79 ± 2.44	12.25 ± 1.72	**25(OH)D**	1	0.155
								T2	14.75 ± 2.38[b]	14.09 ± 2.65	15.40 ± 2.62	**Interaction[2]**	2	0.350
CS-31 Couple Relations Domain	4.50 ± 1.38	4.80 ± 1.23	-0.306	-2.868	2.256	0.055	0.815			5.12 ± 1.51	5.40 ± 1.31			
								T0	4.31 ± 1.81	5.42 ± 2.05	3.21 ± 1.87	**Time points**	2	0.750
								T1	5.30 ± 1.51	3.84 ± 2.38	6.77 ± 1.46	**25(OH)D**	1	0.831
								T2	6.17 ± 1.86	6.11 ± 2.00	6.22 ± 2.04	**Interaction[2]**	2	0.126

Table 3 (continued)

PRO Instrument	Baseline ($n=89$)							Longitudinal phase[1] ($n=38$)					
	25(OH)D		β	95% CI		Wald Chi-square	*p	Time points	25(OH)D		Model Effects Test		
	< 75 nmol/L	≥ 75 nmol/L		Lower	Upper				< 75 nmol/L	≥ 75 nmol/L	Effects	Df	**p
CS-31 Vasomotor Subdomain	9.62 ± 1.17	9.40 ± 1.04	0.216	-1.950	2.381	0.038	0.845		9.04 ± 1.30[a]	5.90 ± 1.12[b]			
								T0 7.07 ± 1.56	7.73 ± 1.75	6.41 ± 1.62	**Time points**	2	0.774
								T1 8.02 ± 1.34	9.80 ± 2.16	6.24 ± 1.28	**25(OH)D**	1	**0.007**
								T2 7.33 ± 1.60	9.60 ± 1.71	5.06 ± 1.75	**Interaction[2]**	2	0.108
CS-31 Health Subdomain	11.62 ± 1.34	13.01 ± 1.19	-1.393	-3.878	1.091	1.208	0.272		9.18 ± 1.79	8.05 ± 1.61			
								T0 9.46 ± 2.08	9.86 ± 2.46	9.05 ± 2.10	**Time points**	2	0.807
								T1 8.80 ± 1.57	8.95 ± 2.18	8.66 ± 1.56	**25(OH)D**	1	0.464
								T2 7.58 ± 2.22	8.74 ± 2.65	6.43 ± 2.53	**Interaction[2]**	2	0.831
CS-31 Aging Subdomain	15.02 ± 1.92	17.38 ± 1.71	-2.356	-5.921	1.208	1.679	0.195		14.24 ± 1.98	12.89 ± 1.78			
								T0 12.42 ± 2.43	12.88 ± 2.75	11.96 ± 2.50	**Time points**	2	0.804
								T1 13.61 ± 1.87	13.36 ± 2.51	13.85 ± 1.83	**25(OH)D**	1	0.372
								T2 14.66 ± 2.51	16.47 ± 2.70	12.84 ± 2.72	**Interaction[2]**	2	0.364
CS-31 Aching in muscles and/or joints	3.38 ± 0.34	3.90 ± 0.32	-0.514	-1.114	0.085	2.828	0.093		3.47 ± 0.38	2.99 ± 0.31			
								T0 3.15 ± 0.45	3.07 ± 0.52	3.24 ± 0.46	**Time points**	2	0.917
								T1 3.32 ± 0.38	3.81 ± 0.62	2.82 ± 0.36	**25(OH)D**	1	0.150
								T2 3.23 ± 0.45	3.54 ± 0.49	2.92 ± 0.50	**Interaction[2]**	2	0.126

* Generalized linear models (GLzM) ** General Mixed Model (GMM); Data adjusted for age, education level, income, usage time of aromatase inhibitors and body mass index. Time point: T0, Baseline; *T1* Intermediate period, corresponding to 12 months after T0; and T2, Final follow-up period, corresponding to 24 months after T0, *PRO Instrument* Patient-Reported Outcome Instrument, *25(OH)D* 25-hydroxyvitamin D, *HADS-A* Hospital Anxiety and Depression Scale, subscale anxiety; HADS-D: Hospital Anxiety and Depression Scale, subscale depression; *HAQ* Health Assessment Questionnaire, *CS-31* 31-item Cervantes Scale, *SD* Standard deviation, *Df* degrees of freedom. Significant Model Effects Test are in bold. Sidak test: Different superscript letters represent statistical significance when comparing pairs, p value < 0.05. [1]Longitudinal phase: PRO Instruments are shown as mean ± SD; [2]Interaction between FACIT-F TOI and time points of study

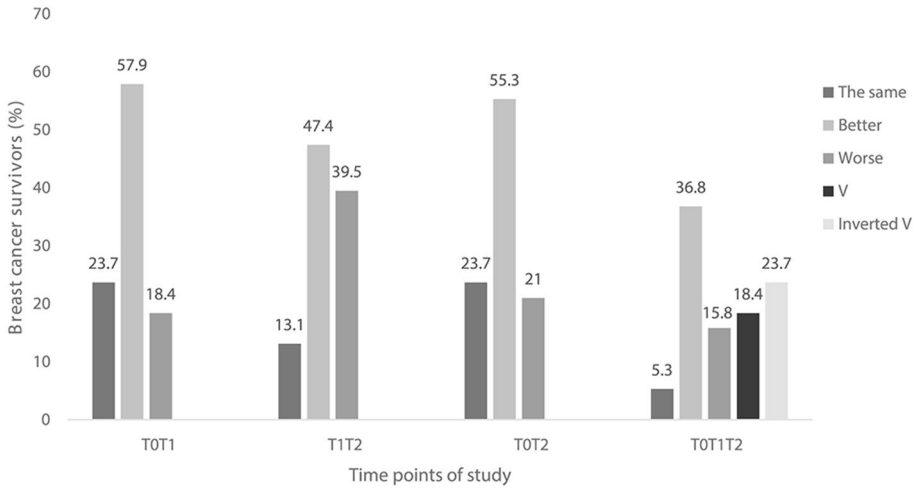

Fig. 1 Distribution of breast cancer survivors in the FACIT-Fatigue clusters throughout the study ($n = 38$). Clusters developed from the 5% MCID between T0T1, T1T2, T0T2 and T0T1T2: The same, Patients who maintained the FACIT-Fatigue score between T0T1, T1T2, T0T2 or who maintained the score at all three times (T0T1T2); Better, Patients who improved the FACIT-Fatigue score between T0T1, T1T2, T0T2 or who improved at T1 and again at T2 (T0T1T2); Worse, Patients who worsened the FACIT-Fatigue score between T0T1, T1T2, T0T2 or who worsened at T1 and again at T2 (T0T1T2); V, Patients who worsened the FACIT-Fatigue score at T1 and improved at T2 (T0T1T2); Inverted V, Patients who improved the FACIT-Fatigue score at T1 and worsened at T2 (T0T1T2). Chi-square Independence Test showed that there was no association between time points of study and clusters, considering T0T1 and T1T2 [$X2(2) = 4.452$; $p = 0.108$]

dietary intake of vitamin D did not differ significantly between the 25(OH) D levels subgroups, however none of the women reached the EAR of this nutrient. There were negative associations between the FACIT-Fatigue score and body adiposity (BMI, WC, WHtR, body fat and conicity index). The greater percentage of women was classified as "better", i.e. with improvement in the FACIT-Fatigue score throughout the study. No significance was found regarding the direct and reverse causality in the association between 25(OH)D concentration and CRF. As for PRO Instruments, lower 25(OH)D level had a negative effect on the scores of anxiety, Menopause and Health domain, and Vasomotor subdomain. In addition, those women with clinically relevant CRF presented more anxiety, depression, functional disability, muscle/joint aches, worse HRQL and worse score in the following domains and subdomains of the CS-31 – Menopause and health, Psychological, Vasomotor, Health, Aging and Couple Relations. These results confirm our initial hypothesis and show the clinical relevance of both 25(OH)D and CRF, highlighting the latter.

Many factors may influence the bioavailability of vitamin D, such as changes in the physiochemical state of this vitamin, complexity of the food matrix, interaction of the vitamin D with other fat-soluble compounds and individual factors [58]. In our study, the 25(OH)D level was positively associated with the MUFA/PUFA ratio and negatively associated with omega-6 intake, which is similar to results found in a study that investigated the change in 25(OH)D level after vitamin D supplementation in healthy older adults [59]. Dawson-Hughes and colleagues identified that the presence of fat in meals increased the absorption of vitamin D from a supplement, but they did not find influence of MUFA/PUFA ratio [60]. The mechanisms proposed by Hollander and colleagues suggest that long-chain fatty acids (oleic and linoleic acids) increase micelle size, impairing the passive diffusion of vitamin D through enterocytes, unlike short (butyric acid) and medium-chain fatty acids (octanoic acid), which are water soluble and do not require micellar formation for their absorption [61]. Although these authors found that the greater degree of unsaturation of fatty acids slowed the rate of vitamin D absorption in the gut [61], more evidence is needed to confirm and explain the mechanism by the MUFA/PUFA ratio would influence the 25(OH)D level.

The dietary intake of vitamin D is commonly low among BC women (mean 4.7 μg/day [62]), as we identified in our study, in which the mean intake of this nutrient was 3.7 ± 1.7 μg/day. A meta-analysis including 10 prospective cohort studies and totalizing 22,341 BC incident cases identified that the lowest categories of vitamin D intake presented a mean below 148 IU/day (3.7 μg/day) [63]. The Recommended Dietary Allowances (RDA) for females until 70 years of age is 15 μg/day and older is 20 μg/day, reference values assuming minimal sun exposure [57]. Food is not the unique source of 25(OH) D, being the serum concentration strongly influenced

Table 4 Associations and effects of anthropometric and body composition parameters on cancer-related fatigue

Independent variable[1]	Baseline ($n=89$)								Longitudinal phase ($n=38$) FACIT-Fatigue (Mean ± SD)						
	FACIT-Fatigue		*p*	β	95% CI		Wald Chi-Square	**p*	Independent Variable		Time points			Model Effects Test		
	Score < 34 ($n=32$)	Score ≥ 34 ($n=57$)			Lower	Upper					T0	T1	T2	Effects	Df	***p*
BMI (Kg/m²)	30.5 (26.3–34.9)	26.8 (25.1–30.1)	**0.002**‡	-0.637	-0.986	-0.287	12.760	**< 0.001**	**BMI (Kg/m²)**		36.64 ± 2.75	39.01 ± 2.11	40.45 ± 2.86	**Time points**	2	0.547
									Without overweight	37.07 ± 2.68	36.58 ± 3.45	36.32 ± 2.86	38.31 ± 3.32	**BMI**	1	0.223
									Overweight	40.33 ± 2.20	36.69 ± 2.76	41.71 ± 2.27	42.59 ± 3.18	**Interaction²**	2	0.083
WC (cm)	98.0 (88.6–102.9)	90.5 (82.0–95.0)	**0.004**‡	-0.265	-0.427	-0.103	10.310	**0.001**	**WC (cm)**		40.94 ± 2.92	45.65 ± 2.87	42.30 ± 3.06	**Time points**	2	0.137
									< 80	46.98 ± 3.00[a]	44.80 ± 3.82	51.75 ± 4.61	44.40 ± 3.81	**WC**	1	**0.001**
									≥ 80	38.94 ± 2.04[b]	37.08 ± 2.67	39.55 ± 2.06	40.21 ± 2.91	**Interaction²**	2	0.243
WHR	0.91 (0.07)	0.9 (0.1)	0.214†	-19.649	-49.249	9.951	1.693	0.193	**WHR**		37.78 ± 2.70	40.27 ± 2.14	41.03 ± 2.91	**Time points**	2	0.513
									≤ 0.85	40.52 ± 2.32	38.44 ± 3.11	41.29 ± 2.68	41.82 ± 3.22	**WHR**	1	0.402
									> 0.85	38.87 ± 2.24	37.13 ± 2.82	39.25 ± 2.27	40.23 ± 3.18	**Interaction²**	2	0.964
WHtR	0.6 (0.6–0.7)	0.6 (0.5–0.6)	**0.002**‡	-41.972	-67.155	-16.788	10.670	**0.001**	**WHtR**		38.83 ± 3.50	44.29 ± 2.92	41.87 ± 3.63	**Time points**	2	0.196
									< 0.5	43.77 ± 3.95	39.91 ± 5.46	48.78 ± 4.77	42.61 ± 5.60	**WHtR**	1	0.249
									≥ 0.5	39.56 ± 2.03	37.75 ± 2.66	39.79 ± 2.06	41.13 ± 2.88	**Interaction²**	2	0.329
Body Fat (Kg)	31.5 (25.2–40.2)	27.7 (23.4–32.9)	0.092‡	-0.285	-0.526	-0.045	5.393	**0.020**	**Body Fat (Kg)**		38.79 ± 2.94	40.76 ± 2.39	39.59 ± 3.32	**Time points**	2	0.348
									≤ 28.21	40.04 ± 2.45	40.42 ± 3.27	40.04 ± 2.71	39.67 ± 3.34	**Body Fat (Kg)**	1	0.770
									> 28.21	39.39 ± 2.70	37.16 ± 3.25	41.48 ± 2.74	39.51 ± 3.94	**Interaction²**	2	0.259
Body Fat (%)	41.2 (36.9–47.8)	40.0 (36.8–43.7)	0.271‡	-0.322	-0.718	0.074	2.543	0.111	**Body Fat (%)**		38.61 ± 2.94	41.04 ± 2.38	40.53 ± 3.28	**Time points**	2	0.384
									≤ 40.35	39.56 ± 2.46	39.18 ± 3.24	40.26 ± 2.72	39.23 ± 3.33	**Body Fat (%)**	1	0.627
									> 40.35	40.56 ± 2.59	38.03 ± 3.23	41.82 ± 2.68	41.83 ± 3.83	**Interaction²**	2	0.539
Conicity Index	1.3 (0.1)	1.3 (0.1)	0.152†	-20.073	-45.098	4.953	2.471	0.116	**Conicity Index**		36.79 ± 2.73	39.54 ± 2.13	40.13 ± 2.95	**Time points**	2	0.409

Table 4 (continued)

Independent variable[1]	Baseline ($n=89$)							Longitudinal phase ($n=38$) FACIT-Fatigue (Mean ± SD)						
	FACIT-Fatigue		*p*	β	95% CI		Wald Chi-Square	*p	Independent Variable	Time points			Model Effects Test		
	Score < 34 ($n=32$)	Score ≥ 34 ($n=57$)			Lower	Upper				T0	T1	T2	Effects	Df	**p
									≤ 1.3	40.62 ± 2.18[a]	39.21 ± 2.84	40.49 ± 2.41	42.18 ± 3.08	**CI**	1	**0.021**
									> 1.3	37.01 ± 2.29[b]	34.36 ± 3.03	38.59 ± 2.34	38.08 ± 3.17	**Interaction[2]**	2	0.475

[†] Test-t Independent; [‡]Mann–Whitney; Continuous variables are shown as mean (standard deviation) or median (p25-p75); *Generalized linear models (GLzM); **General Mixed Model (GMM); Data adjusted for age, education level, income and usage time of aromatase inhibitors. FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy—Fatigue Scale, with cut-off < 34 indicating cancer-related fatigue; Time point: T0, Baseline; T1, Intermediate period, corresponding to 12 months after T0; and T2, Final follow-up period, corresponding to 24 months after T0; SD, Standard deviation; Df, degrees of freedom; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio. Significant Model Effects Test are in bold. Sidak test: Different superscript letters represent statistical significance when comparing pairs, p value < 0.05.
[1]Continuous variable. [2]Interaction between anthropometric/ body composition parameters and time points of study. The variables Body Fat and Conicity Index were categorized by the medians

Table 5 Associations and effects of cancer-related fatigue on PRO instruments

PRO Instrument	Baseline ($n=89$)							Longitudinal phase[1] ($n=38$)					
	FACIT-Fatigue		β	95% CI		Wald Chi-square	*p	Time points		FACIT-Fatigue		Model Effects Test	
	Score < 34	Score ≥ 34		Lower	Upper					Score < 34	Score ≥ 34	Effects	Df	**p
HADS-A	10.94 ± 0.98[a]	7.16 ± 0.86[b]	-3.779	-5.498	-2.059	18.546	**< 0.001**			8.21 ± 1.11[a]	6.57 ± 0.89[b]			
								T0	9.33 ± 1.15[a]	10.43 ± 1.25	8.22 ± 1.17[a]	**Time points**	2	**0.035**
								T1	6.91 ± 0.96[b]	7.56 ± 1.22	6.26 ± 0.90[b]	**FACIT-Fatigue**	1	**0.028**
								T2	5.94 ± 1.38[a,b]	6.63 ± 1.72	5.25 ± 1.31[a,b]	**Interaction[2]**	2	0.602
HADS-D	10.15 ± 1.00[a]	5.35 ± 0.88[b]	-4.799	-6.559	-3.038	28.544	**< 0.001**			8.22 ± 1.19[a]	6.61 ± 0.98[b]			
								T0	7.50 ± 1.29	8.59 ± 1.40	6.42 ± 1.32	**Time points**	2	0.697
								T1	7.15 ± 1.06	7.79 ± 1.31	6.50 ± 1.00	**FACIT-Fatigue**	1	**0.027**
								T2	7.60 ± 1.47	8.30 ± 1.72	6.91 ± 1.41	**Interaction[2]**	2	0.676
HAQ	1.39 ± 0.14[a]	0.83 ± 0.12[b]	-0.554	-0.803	-0.304	18.947	**< 0.001**			1.02 ± 0.16[a]	0.76 ± 0.13[b]			
								T0	0.81 ± 0.17	0.95 ± 0.19	0.68 ± 0.18	**Time points**	2	0.614
								T1	0.86 ± 0.14	1.00 ± 0.18	0.71 ± 0.13	**FACIT-Fatigue**	1	**0.022**
								T2	0.99 ± 0.20	1.10 ± 0.24	0.89 ± 0.18	**Interaction[2]**	2	0.907
CS-31 Total Score	94.20 ± 5.88[a]	59.87 ± 4.86[b]	-34.337	-45.278	-23.397	37.839	**< 0.001**			72.10 ± 8.33[a]	57.24 ± 6.88[b]			
								T0	65.76 ± 9.17	76.13 ± 10.02	55.38 ± 9.36	**Time points**	2	0.545
								T1	62.05 ± 7.21	65.61 ± 9.01	58.49 ± 6.94	**FACIT-Fatigue**	1	**0.007**
								T2	66.21 ± 9.94	74.57 ± 11.66	57.84 ± 9.61	**Interaction[2]**	2	0.219
CS-31 Menopause and Health Domain	50.00 ± 3.08[a]	32.86 ± 2.55[b]	-17.143	-22.882	-11.405	34.284	**< 0.001**			35.17 ± 4.08[a]	29.25 ± 3.21[b]			
								T0	30.45 ± 4.19	33.76 ± 4.72	27.14 ± 4.35	**Time points**	2	0.771
								T1	31.83 ± 3.40	32.98 ± 4.44	30.69 ± 3.26	**FACIT-Fatigue**	1	**0.042**
								T2	34.36 ± 4.95	38.78 ± 6.08	29.93 ± 4.70	**Interaction[2]**	2	0.385
CS-31 Psychological Domain	26.25 ± 2.46[a]	10.03 ± 2.03[b]	-16.214	-20.792	-11.636	48.180	**< 0.001**			15.89 ± 3.41[a]	9.60 ± 2.76[b]			
								T0	17.52 ± 3.68	24.11 ± 4.05[a]	10.94 ± 3.78	**Time points**	2	0.060
								T1	10.60 ± 2.92	11.48 ± 3.81[b]	9.71 ± 2.79	**FACIT-Fatigue**	1	**0.008**
								T2	10.11 ± 3.94	12.09 ± 4.74[a,b]	8.14 ± 3.78	**Interaction[2]**	2	**0.004**
CS-31 Sexuality Domain	12.78 ± 1.58	12.53 ± 1.30	-0.250	-3.183	2.683	0.028	0.867			13.27 ± 2.29	12.29 ± 1.84			
								T0	11.82 ± 2.46	11.69 ± 2.73	11.95 ± 2.53	**Time points**	2	0.541
								T1	12.20 ± 1.95	12.45 ± 2.51	11.96 ± 1.87	**FACIT-Fatigue**	1	0.530
								T2	14.32 ± 2.68	15.66 ± 3.24	12.98 ± 2.56	**Interaction[2]**	2	0.494
CS-31 Couple Relations Domain	5.08 ± 1.46	4.49 ± 1.20	-0.591	-3.302	2.120	0.182	0.669			9.27 ± 1.79[a]	6.17 ± 1.48[b]			

Table 5 (continued)

PRO Instrument	Baseline ($n=89$)							Longitudinal phase[1] ($n=38$)					
	FACIT-Fatigue		β	95% CI		Wald Chi-square	*p	Time points	FACIT-Fatigue		Model Effects Test		
	Score < 34	Score ≥ 34		Lower	Upper				Score < 34	Score ≥ 34	Effects	Df	**p
								T0	6.31 ± 1.96	7.52 ± 2.13	5.10 ± 2.01	**Time points**	2	0.355
								T1	8.47 ± 1.56	10.34 ± 2.06	6.59 ± 1.50	**FACIT-Fatigue**	1	**0.008**
								T2	8.38 ± 2.05	9.95 ± 2.40	6.81 ± 1.99	**Interaction[2]**	2	0.766
CS-31 Vasomotor Subdomain	11.02 ± 1.20[a]	8.74 ± 0.99[b]	-2.279	-4.509	-0.050	4.015	**0.045**			7.28 ± 1.68[a]	6.80 ± 1.33[b]			
								T0	6.59 ± 1.78	6.56 ± 1.99	6.63 ± 1.85	**Time points**	2	0.922
								T1	7.15 ± 1.42	7.11 ± 1.92	7.19 ± 1.36	**FACIT-Fatigue**	1	0.684
								T2	7.37 ± 1.90	8.16 ± 2.36	6.58 ± 1.81	**Interaction[2]**	2	0.647
CS-31 Health Subdomain	16.75 ± 1.17[a]	10.42 ± 0.97[b]	-6.325	-8.513	-4.138	32.115	**< 0.001**			11.30 ± 1.92[a]	7.91 ± 1.47[b]			
								T0	9.87 ± 1.98	12.36 ± 2.26	7.40 ± 2.06	**Time points**	2	0.502
								T1	8.83 ± 1.58	9.07 ± 2.12	8.59 ± 1.51	**FACIT-Fatigue**	1	**0.019**
								T2	10.12 ± 2.20	12.48 ± 2.84	7.76 ± 2.06	**Interaction[2]**	2	0.097
CS-31 Aging Subdomain	22.24 ± 1.74[a]	13.70 ± 1.44[b]	-8.539	-11.777	-5.301	26.721	**< 0.001**			17.19 ± 2.25[a]	14.09 ± 1.85[b]			
								T0	14.29 ± 2.47	15.40 ± 2.71	13.19 ± 2.52	**Time points**	2	0.727
								T1	15.66 ± 1.94	17.26 ± 2.39	14.07 ± 1.87	**FACIT-Fatigue**	1	**0.036**
								T2	16.97 ± 2.72	18.92 ± 3.22	15.02 ± 2.62	**Interaction[2]**	2	0.765
CS-31 Aching in muscles and/or joints	4.19 ± 0.35[a]	3.41 ± 0.31[b]	-0.779	-1.394	-0.165	6.176	**0.013**			3.79 ± 0.49	3.29 ± 0.39			
								T0	3.33 ± 0.51	3.25 ± 0.56	3.41 ± 0.52	**Time points**	2	0.502
								T1	3.40 ± 0.44	3.73 ± 0.60	3.07 ± 0.41	**FACIT-Fatigue**	1	0.110
								T2	3.89 ± 0.56	4.40 ± 0.67	3.39 ± 0.53	**Interaction[2]**	2	0.057

[*] Generalized linear models (GLzM); **General Mixed Model (GMM); Data adjusted for age, education level, income, usage time of aromatase inhibitors and body mass index. FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy—Fatigue Scale, with cut-off < 34 indicating cancer-related fatigue; Time point: T0, Baseline; T1, Intermediate period, corresponding to 12 months after T0; and T2, Final follow-up period, corresponding to 24 months after T0; PRO Instrument, Patient-Reported Outcome Instrument; HADS-A: Hospital Anxiety and Depression Scale, subscale anxiety; HADS-D: Hospital Anxiety and Depression Scale, subscale depression; HAQ, Health Assessment Questionnaire; CS-31, 31-item Cervantes Scale; SD, Standard deviation; Df, degrees of freedom. Significant Model Effects Test are in bold. Sidak test: Different superscript letters represent statistical significance when comparing pairs, p value < 0.05. [1]Longitudinal phase: PRO Instruments are shown as mean ± SD; [2]Interaction between FACIT-Fatigue and time points of study

by direct exposure of the skin to sunlight [64]. However, some factors may influence the sun induced synthesis, among which the season, which influenced the 25(OH) D levels in the present study; time of day; latitude; altitude; air pollution; skin pigmentation; sunscreen; aging; sunlight passing through glass and plastic [64]. Moreover, some individuals are exposed to very limited amounts of solar ultraviolet radiation, making them dependent on an adequate oral intake of this vitamin, in order to favor optimal 25(OH)D levels [65–67]. Amrein and colleagues [68] defend the importance of vitamin D supplementation in certain risk groups and the vitamin D food fortification as a worldwide public health strategy to avoid severe vitamin D deficiency.

Although there is no consensus regarding the optimal 25(OH)D level in the body, the SBEM and SBPC in a position statement about the reference values, identify the potential benefits of maintaining 25(OH)D levels above 75 nmol/L in specific conditions, reference value in accord with the Endocrine Society [69]. Among the specific conditions, we highlight the elderly, individuals with cancer and using drugs with the potential to affect the vitamin D metabolism, characteristics present in our sample [42]. Moreover, the use of AIs (letrozole and exemestane) could also increase the requirements for this vitamin, considering that they are metabolized in the liver by the CYP3A4 system [70] and the vitamin D induce the expression of these genes [71]. In our study, the median 25(OH)D level was 84 nmol/L (range 18.5 – 137.3 nmol/L) and 39.3% ($n=35$) presented 25(OH)D levels below 75 nmol/L, similar result to the study of Friedman and colleagues, in which the median was 87.5 nmol/L (range 17 – 232.9 nmol/L) and 35% ($n=136$) of postmenopausal BC survivors presented level < 75nmoL/L [72]. According to the US Institute of Medicine, 25(OH)D levels equal to or above 50 nmol/L is sufficient for practically all persons for proper functioning of the calcium-phosphate metabolism and to maintain bone density and there would be no increased benefit in 25(OH)D levels above 75 nmol/L [57]. However, evidence suggest potential additional benefits for levels above 75 nmol/L as a reduction in the risk of fractures [42] and falls, better tooth attachment, improved depression and wellbeing [8], reduction of the risk of autoimmune diseases, type 2 diabetes, cardiovascular disease, infectious diseases [69] and neoplastic diseases [8, 69]. High 25(OH)D levels were significantly associated with lower BC mortality (> 72.75 vs < 52.5 nmol/L, pooled RR = 0.58, 95% CI: 0.40–0.85), overall mortality (> 68.75 vs < 51.75 nmol/L, pooled RR = 0.61, 95% CI: 0.48–0.79) and BC recurrence (> 67.25 vs < 36.75 nmol/L, pooled RR = 0.61, 95% CI: 0.47–0.80) [63]. Calcitriol (1,25-dihydroxyvitamin D3), the active metabolite of vitamin D, present anticancer actions as cell cycle arrest, stimulation of apoptosis and inhibition of invasion, metastasis and angiogenesis, inhibiting the growth of malignant cells including BC cells [73].

Cancer treatment-induced bone loss is a common side effect in BC women [74]. The prevalence of BC women undergoing AI with adequate bone health and vitamin D status is very low, only 5.6%, which justifies the monitoring of these parameters during and even after treatment [74]. The depletion of estrogen resulting from the AI treatment may cause an accelerated decrease in bone mineral density (BMD), which is the primary cause of the increased fracture risk [75]. Patients with a high risk of fractures [75] and, or patients receiving antiresorptive drugs for cancer treatment induced bone loss, may benefit from pharmacological intervention that contribute to the preservation of bone health [74], such as vitamin D supplementation. However, although vitamin D supplementation is one of the most frequent therapies indicated to women with postmenopausal osteoporosis presenting slow BMD loss, this therapy may not be effective for the prevention of accelerated BMD loss derived from AI use [75].

Endocrine therapy is recommended for a minimum of 5 years. The option of extended endocrine therapy (EET), either with 10 years of tamoxifen or 5 years of an AI after 4.5 to 6 years of tamoxifen, has been increasingly recommended. The use of 10 years of AI has been disfavored because of the adverse event profile [76]. Although the EET with AI is associated with increased risk of bone-related toxic effects, cardiovascular events, hot flashes, arthralgia and myalgia, the EET did not increase the risk of other adverse effects, such as fatigue [77]. In our study, at baseline, the women with longer median time using AI did not present CRF and, considering the longitudinal phase, most women were classified as "better", i.e. with improvement in FACIT-Fatigue score throughout the study. It is noteworthy that at baseline, only three women (3.4%) were on EET, i.e., in use AI beyond 5 years of therapy, already in T2, 14 women (36.8%) were on EET.

In the present study, indicators of greater body adiposity were negatively associated with the FACIT-Fatigue score, i.e., with higher CRF. Adipose tissue is a metabolically very active endocrine tissue that influences the inflammatory process [78], which was the mechanism used to explain greater CRF in obese BC patients [79]. BMI, sedentary lifestyle and nutritional deficiencies are some of risk factors associated with chronic inflammation, which have potential to generate a pre-treatment inflammatory state and even pre-treatment fatigue, identified as the principal predictor of CRF [80]. However, various mechanisms are involved in its pathophysiology, such as changes in adenosine triphosphate and muscle metabolism,

neurotransmitter dysregulation, hypothalamic–pituitary–adrenal axis disruption, and neural-immune signaling triggered by inflammation [80, 81], and CRF may occurs even among patients without risk factors [80], remaining in progress investigations regarding its etiology.

The causal effect of body adiposity on the CRF cannot be confirmed in the present study, yet the result is alarming considering that obesity and abdominal visceral adipose tissue accumulation are associated with metabolic consequences and risk of cardiovascular disease (CVD), the latter being the leading cause of death in postmenopausal women [82] and also in BC survivors [83]. Furthermore, antineoplastic treatment, including endocrine therapy, may favor cardiotoxicity [84]. Mazzutti and colleagues [30] identified in the same sample of the present study, that women in AI use had a significant number of risk factors for CVD. Considering only the risk factor "body adiposity", it is reasonable to infer that women with CRF would be at increased risk of metabolic syndrome and other cardiovascular disorders when compared to those without CRF, which deserves further consideration.

The CRF affects 50% to 90% of cancer patients regardless of age, sex or diagnosis [85], persisting after the end of treatment [86, 87] and presenting emotional, physical, cognitive, functional consequences, in addition to causing uncertainty and impact the sense-of-self [88]. In the present study, CRF was associated with practically all health outcomes investigated, being relevant result for clinical practice and reinforces the need for more studies aimed at the development of effective interventions to control this adverse effect whit high potential for better the HRQL and associated aspects.

Testing and correction of 25(OH)D levels are commonly studied in cases of fatigue [7, 89–93], but more studies are needed to prove the effectiveness of vitamin D supplementation in reducing or preventing of the CRF. The VICTORIA study aims to confirm this association through a randomized controlled trial [94]. A recent genetic analysis between low 25(OH)D levels and fatigue showed little evidence of a causal effect, suggesting an unlikely protective effect of 25(OH)D on fatigue, but considering a lifelong exposure to a low serum concentration, unlike observational or intervention studies which investigate the association between short-term changes in 25(OH)D concentration and fatigue [95]. Havdahl, Paternoster and Smith [95] believe that there is a reverse causality between fatigue and 25(OH)D levels, and that this last could be just one marker or consequence of fatigue, considering that fatigued individuals tend to sedentary lifestyle and longer stay indoors without exposure to the sun. In addition, these authors emphasize that fatigue and 25(OH)D deficiency have risk factors in common, which can favor misinterpretations without proper adjustments [95]. In our prospective study, there was no significant causality between 25(OH)D levels and CRF, but the effect of both on important aspects of HRQL in BC survivors is notable, therefore not disregarding the favorable effects of a possible supplementation of vitamin D in this population.

We must consider some limitations, as a small sample size and sample loss during follow-up. Furthermore, the assessment of food consumption from 24HR is subject to memory bias, although the interviews were conducted by nutritionists to minimize this risk. Pharmaceutical history might influence functional outcomes and improve the sample characterization, but unfortunately these data were not collected completely. In addition, the PRO Instruments used in this study are self-reported questionnaires, however all participants replied by interview, which may have inhibited responses to certain items. This standardization was necessary considering there were illiterate women in our sample, being the interviews conducted by properly trained researchers. Due to the intrinsic limitations of a monocentric design, these results cannot be generalized for the general population, although they are relevant and may be useful in the elaboration of hypotheses for future larger studies and multicentric investigations. A strength of this study is the assessment of CRF, 25(OH)D, anxiety, depression, functional disability, muscle/joint aches, HRQL and related aspects at three time points, with a 2-year follow-up. Furthermore, to the best of our knowledge, this is the first study to assess both the association and the effect of vitamin D and CRF on several aspects related to the health of BC survivors using AI.

Maintaining quality of life and fatigue were the principal global issue and the specific symptom, respectively, identified by BC patients [96]. However, the fatigue is underreported as cancer patients frequently associate this complication with disease progression or treatment ineffectiveness rather than as an adverse effect of treatment, and the fear of progression inhibits reporting [17]. In addition, some physicians have insufficient knowledge about CRF, available pharmacologic and nonpharmacologic interventions, as well as their serious consequences on HRQL [85]. This reinforces the need for wide dissemination in academic and scientific environment, counseling both patient and family, and monitoring this adverse effect on oncology medical routine through appropriate instruments, in order to contribute to improving HRQL and health outcomes [17].

Conclusions

The clinical relevance of 25(OH)D and CRF is highlighted, especially of the CRF, considering the consistent impact on several adverse effects often reported by

women in AI use, such as anxiety, depression, functional disability, muscle/joint aches, HRQL, couple relations, psychological symptoms, and related to menopause and health. In addition, it is important to note the negative effect of body adiposity on CRF. Strategies that comprise emotional support, physical exercise, and nutritional guidance need to be included in routine care of BC survivors during adjuvant endocrine therapy. More studies aimed at the development of feasible and effective interventions are awaited.

Abbreviations

24HR: 24-Hour dietary recall; 25(OH)D: 25-Hydroxyvitamin D; AI: Aromatase Inhibitors; AIC: Akaike Information Criterion; BC: Breast cancer; BF: Body fat; BIA: Bioelectrical impedance analysis; BMI: Body mass index; CRF: Cancer-related fatigue; CS : Cervantes Scale; CS-31: 31-Item Cervantes Scale; CVD: Cardiovascular disease; EAR: Estimated Average Requirements; EET: Extended endocrine therapy; FACIT-F: Functional Assessment of Chronic Illness Therapy-fatigue; FACT-G: Functional Assessment of Cancer Therapy-General; GLzM: Generalized Linear Model; GMM: Generalized Mixed Model; HADS: Hospital Anxiety and Depression Scale; HADS-A: Hospital Anxiety and Depression Scale, subscale anxiety; HADS-D: Hospital Anxiety and Depression Scale, subscale depression; HAQ: Health Assessment Questionnaire; HR+: Receptor-positive; HRQL: Health-Related Quality of Life; MCID: Minimum Clinically Important Difference; MUFA: Monounsaturated fatty acids; NDSR: Nutrition Data System for Research; PRO: Patient-reported outcome; PUFA: Polyunsaturated fatty acids; RDA: Recommended Dietary Allowances; SBEM: Brazilian Society of Endocrinology and Metabolism; SBPC: Brazilian Society of Clinical Pathology/Laboratory Medicine; T0: Baseline; T1: Intermediate follow-up period; T2: Final follow-up period; WC : Waist circumference; WHR: Waist-to-hip ratio; WHtR: Waist-to-height ratio.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-022-09962-x.

Additional file 1: Supplementary Table 1. Demographic and clinical characteristics of the breast cancer survivors during endocrine therapy, considering FACIT-Fatigue subgroups.

Additional file 2: Supplementary Table 2. Direct and reverse association between 25(OH)D and cancer-related fatigue.

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Authors' contributions

Conceptualization: IDDC, FSM, MTML, KPC, PPLC, CEP, YCPM; Data curation: IDDC, FSM, MTML, DS, JFC, KPC, CEP, YCPM; Formal analysis: IDDC, FSM, MTML, KPC, CEP, YCPM; Investigation: IDDC, FSM, MTML, DS, JFC, KPC, PPLC; Methodology: IDDC, FSM, MTML, KPC, CEP, YCPM; Resources: CEP, YCPM; Supervision: CEP, YCPM; Visualization: IDDC, FSM, MTML, KPC, PPLC, CEP, YCPM; Writing-original draft: IDDC; Writing-review: IDDC, FSM, MTML, KPC, DS, JFC, PPLC, CEP, YCPM; Editing: IDDC, FSM, MTML, KPC, PPLC, CEP, YCPM. All the authors listed have read and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of Federal University of Uberlandia (nº. 1.331.949/15, addendum nº. 2.905.835/18) and conducted based on the norms of the Declaration of Helsinki. All participants signed a free and informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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