Prevalence and Correlates of Cancer-related Fatigue in Breast Cancer Survivors

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Research Article

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Abstract

Purpose To identify potential correlates of CRF after curative breast cancer (BC) treatment. The hypothesis was that fatigue would be more severe among women treated with cardiotoxic drugs, with poor physical condition and those who exercised less.

Methods Prospective observational cross-sectional design. Fatigue was evaluated through Perform Questionnaire (multi-item, multi-dimensional). Patient-reported assessments and objective information regarding clinical data, physical activity (PA) and physical condition were analysed as potential correlates of CRF.

Results 180 women who remained free of disease were recruited. Prevalence of fatigue interfering with quality of life was 43%. Weight, BMI, treatment with trastuzumab and time spent walking one mile were positively associated with fatigue. Age, time from diagnosis, self-reported walking time, basal and recovery heart rate were negatively associated. Previous chemo, radio or hormonal therapy, objectively assessed weekly PA, cardio-respiratory condition, muscular strength and adherence to Mediterranean diet were not associated with CRF. However, an interesting unexpected negative association with nut intake was found.

Conclusions CRF is a prevalent problem after BC treatment. Objectively assessed PA, cardiorespiratory fitness and muscular strength did not predict CRF. The association of CRF with trastuzumab and low intake of nuts should be confirmed in further studies. A deeper insight in heart rate variability is warranted. Future research should include longitudinal studies and determination of biomarkers.

Implications for Cancer Survivors BC survivors, especially younger and overweight women, should be informed about fatigue as a potential persistent symptom through all stages of the cancer trajectory and into survivorship. They also should be routinely screened for CRF.

Background

Advances in screening, diagnosis, therapies and supportive care along the trajectory of cancer have led to an expected 26 million survivors in 2040 [1]. Cancer-related fatigue (CRF) is a subjective experience which constitutes one of the most common and frustrating symptoms through all stages of the cancer trajectory and into survivorship. It is defined as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity, interferes with usual functioning and is not relieved by rest or sleep [2]. Fatigue is often unrecognized and undertreated by health care professionals. CRF can be a barrier to cancer survivors' return to work [3], has a profound emotional effect on patients and importantly also could have an impact on survival [4]. Prevalence rates for CRF are in the range of 70-80%, but reported rates could depend on the type of cancer [5], gender [6], stage [7], active treatments [8], time from treatment [7], the use of screening methods, type of questionnaire and established threshold to diagnose fatigue.

Some studies suggest fatigue being more frequent in breast cancer (BC) survivors [5, 9,10]. Fatigue in BC survivors has been related to physical [11], psychological [12], social [13], cognitive [14] and behavioural factors [7,15]. Though fatigue is a well-known adverse effect of aromatase inhibitors [16], there is not much information about influence of previous treatments which are potentially cardiotoxic such as anthracyclines, trastuzumab and radiotherapy in BC survivors [7]. Inactivity is one of the commonest correlates for CRF [8, 17]. However, most of the studies used subjective methods such as questionnaires which could overestimate the physical activity (PA) [18]. Also physical deconditioning [19] has been proposed as correlate but there is controversial data [20].

Hence, this study was designed to better define the associations between fatigue in mid-term BC survivors and PA and its consequences such as physical deconditioning. We hypothesized that fatigue would be more severe among women treated with cardiotoxic drugs, with poor physical condition and those who exercised less.

Materials And Methods

Study design

These are two consecutive descriptive cross-section studies (PH-UEM-02, PH-UEM-05). The study protocols were approved by the relevant Ethics Committee and were therefore performed according to the Declaration of Helsinki and European relevant law.

We aimed to answer the following questions: (i) how many disease-free BC patients experience a fatigue which interferes with their quality of life? (ii) is fatigue associated with former treatment modalities? (iii) is fatigue associated with any demographic correlate? (iv) is fatigue associated with physical activity and/or physical condition?

Participants

Candidates were patients older than 18, diagnosed with BC who had finished their treatments (trastuzumab and hormonal therapy were allowed during the evaluation) and were free of disease. They were required to be able to walk a mile. Written informed consent was obtained from all participants. Patients were recruited by the oncologists at the hospital during their follow-up.

Measures

Patient-reported assessments

1. Fatigue

Fatigue was measured using the PERFORM questionnaire (PQ) in the total population.

PQ was developed among Spanish-speaking cancer patients for the assessment of fatigue within usual clinical practice [21]. The score ranges from 12 to 60 (the higher, the less fatigued). The psychometric

properties of the PQ were validated and a change of 3.5 points represented a clinical relevant improvement [21].

PH-UEM-05 study also included FACIT-fatigue (FACIT-F) and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30). FACIT-F is a 13-items questionnaire. The scale range is 0 to 52, with 52 being the best possible score indicating no fatigue.

The EORTC QLQ-C30 also generates a fatigue score. It is a unidimensional scale derived from three items. The scale ranges from 0 to 100, being 100 the worst possible score.

2. Socio-economic characteristics

A self-report questionnaire (table 1) was used to obtain information about habit of smoking, marital status, economic level, education employment status, dependent relatives, and perceived health.

3. Quality of life (QoL)

PH-UEM 05 study included the EORTC QLQ-C30 and EORTC QLQ-BR23. The core questionnaire of EORTC QLQ-C30, contains five functional scales (physical, role, cognitive, emotional and social functioning) and three symptom scales (fatigue, pain and nausea-vomiting). It also contains a scale for global health status and QoL and a number of single items for assessing additional symptoms. QLQ-BR23 instrument is a 23-item, BC specific module of five QoL dimensions. The raw scores are transformed linearly such that all scales range from 0 to 100. A higher score represents a higher level of functioning and for symptom scales a higher level of symptoms.

4. Adherence to Mediterranean diet

PREDIMED is a 14-item questionnaire developed in Spain to assess the adherence to Mediterranean diet. Each of the items is scored 1 or 0. The resulting score ranges from 0 to 14. Scores higher than 7 are considered as good adherence to the Mediterranean diet [22].

5. Physical activity

Disease-related and other objective data

1. Clinical data

Clinical data (table 1) were collected by health practitioners from clinical records.

2. Anthropometry

Body mass index (BMI) was determined as body mass/height squared (kg/m^2). All measurements (waist and hip circumference) were made according to international recommendations.

3. Physical activity

Weekly physical activity was objectively monitored with accelerometers, using a triaxial Actigraph GT3X monitor (Actigraph, Pensacola, FL, USA).

4. Physical condition

Cardiorespiratory fitness was assessed using the one-mile walk test. (MWT) All tests were performed at the hospital and timed using a stopwatch to the nearest 0.1 s. Participants' $VO2_{MAX}$ was calculated according to age, gender and body mass-specific equations detailed elsewhere [24]. Heart rate was measured before and immediately after the tests with a heart rate telemeter. Recovery heart rate was measured one minute after finishing. Participants' handgrip strength was measured using a dynamometer and scores recorded in kilograms (to the nearest 0.1 kg). The sit-to-stand (STS) test, which measures the time (seconds) required to perform five consecutive repetitions of sitting down and uprising from a chair, was used for the assessment of lower-limb strength.

Statistics analysis

Descriptive analysis was performed for patient characteristics in each study separately and in the pooled sample. To investigate bivariate associations, Pearson correlation coefficients and analyses of variance were used. For the results reported, fatigue (measured by PQ) was considered a continuous dependent variable. Having both continuous and categorical predictor variables, ordinary least squares regressions and analysis of covariance (ANCOVA) were estimated. Non-linear effects using quadratic terms were explored for linear predictors and equivalent recodifications when the focus was on nominal or ordinal independent variables. All data analyses were conducted using STATA v15.1 (StataCorp) statistical software.

Results

Descriptive

A total of 180 BC survivors participated. Clinical characteristics are reported in Table 1. The mean age of the total sample was 51 years. Average time from diagnosis of cancer was 28.5 months. 11% were current smokers. On average, they presented a good Mediterranean diet adherence (9.1/14). The majority of women were slightly overweight (BMI 26) with values of central adiposity in the range of normality (waist < 88 cm and waist-to-hip ratio < 0.85). Most patients met PA recommendations (260 minutes per week) but they registered very low levels of vigorous activity (5,5 minutes per week). Regarding physical condition, the mean estimated VO_{2max} was 28 ml/kg/min and handgrip strength 25 kg.

Fatigue and patient-reported assessments (table 2)

1. Consistency among different scales (PERFORM, FACIT and fatigue item/EORTC) was high. In all cases, bivariate correlations were above 0.75 (PQ and FACIT 0.81; PQ and fatigue C30 0.75).
2. Fatigue and sociodemographic data. No associations were found.

3. Fatigue and QoL. The EORTC QLQ-C30 scores can be found in table 1. The association between fatigue and quality of life (EORTC global) reached a correlation of 0.7 (Supplementary Figure 1). The functional scales were significantly correlated to fatigue. Also, they were nausea, pain, dyspnoea, appetite loss and financial difficulties. QLQ-BR23 revealed significant associations: body image, breast symptoms, arm symptoms, future perspective, systemic side effects and hair loss. The threshold to consider fatigue as significant was the point (PQ= 45.8) from which QoL was worse than expected for Spanish population according to normative data (EORTC Global 66,8) (Supplementary Figure 1). Patients who scored less than 45.8 in the PQ were considered to have a clinically significant CRF.

Prevalence of fatigue. 43% patients had a PQ score inferior to 45.8 and were therefore considered to have a clinically significant fatigue. 9% of women did not report any fatigue (maximum score-60).

4. Fatigue and adherence to Mediterranean diet. We did not find any association between fatigue and adherence to Mediterranean diet. We analysed the association for each of the items, finding a significant association between item 12^{th} and fatigue. Item 12^{th} values the intake of 30 g of nuts three or more times per week.
5. Fatigue and self-reported PA (IPAQ). Patients who reported more time walking (low intensity) in the last seven days, were less fatigued.

Fatigue and objective data (tables 3, 4)

Fatigue and age: Younger women reported more fatigue.

Fatigue and anthropometry: Weight, BMI and hip perimeter were associated with fatigue.

Fatigue and clinical data: A longer time from diagnosis was associated with less CRF. Among treatments, only trastuzumab was associated with CRF.

Fatigue and PA. Objectively assessed physical activity (moderate, vigorous and sedentary time were explored) was not related to CRF scores.

Fatigue and physical condition. Physical condition measured as estimated cardiorespiratory condition ($VO2_{MAX}$), upper and lower muscular strength was not associated with fatigue. Fatigue was positively associated with the time required to walk a mile, with the basal heart rate and recovery heart rate.

Discussion

Patient reported outcomes (PROs) of which, CRF is a good representative, are a critical element of patient-centered care, since they provide a direct measurement of patient experiences [25] and also have a prognostic value [4]. We have confirmed that CRF is a prevalent condition among BC survivors after finishing their treatment. In our sample, almost half of BC survivors reported a clinically significant score of fatigue. Contrary to the expected, objectively assessed PA and previous treatment with anthracyclines,

hormone or radiotherapy were not associated with CRF. Objective tests for evaluating physical condition such as MWT, sit-to-stand and handgrip did not predict fatigue either. We found as correlates for having fatigue after treatment: being younger, higher weight and BMI, gait speed, previous therapy with trastuzumab, less time elapsed from diagnosis, reporting less walking time, having typical side effects and symptoms such as pain, dyspnea or appetite loss, having a poorer body image, having financial difficulties, cancer-related uncertainty and scoring lower in the functional scales of the EORTC-QLQ-C30 questionnaire. Though adherence to the Mediterranean diet did not predict CRF, the intake of nuts seemed to protect against fatigue. Some correlates could be interpreted as potential cause of fatigue such as weight or trastuzumab, whereas others seem to be symptoms that co-ocurred such as pain or dyspnea. It is very well known the presentation of fatigue as symptom cluster [26]. But a role of these symptoms triggering or maintaining fatigue cannot be excluded.

Diagnosis of CRF depends on how active its search through systematic screening is. Despite of recommendations by guidelines [27], systematic assessment of fatigue is not being done during the follow-up of adult cancer survivors. As many others, our study shows considerable variability in fatigue suggesting that some patients are at a particular risk for experiencing fatigue whereas 9% did not report any fatigue at all. In order to estimate fatigue prevalence we considered fatigue as clinically significant, if it interfered with QoL (Supplementary Figure 1) [28]. It is remarkable that the mean score of QoL in this cohort of BC survivors (68.9) is over the expected for the general Spanish population (66.8) and also for 50-59 year-old Spanish women (62.6) [28].

The ideal scale to evaluate CRF is not established and may be population dependant [29]. Multidimensional scores offer a more comprehensive assessment by capturing multiple characteristics of fatigue. The choice of the PQ multidimensional scale was based on the fact that it was originally developed among Spanish-speaking cancer patients, showed good psychometric properties, exhibited good completion rates and had a known sensitivity to change [21]. The comparison of PQ scores with other measures (FACIT, fatigue item in the EORTC QLQ-C30, the global EORTC QLQ score) revealed strong correlations. It is noteworthy that the mean score in the unidimensional fatigue item of the EORTC QLQ-C30 (22) was quite similar to the expected value for the general population in our country (23.9, considering the sample was constituted only by women) [28].

CRF cannot be entirely explained by characteristics of the disease and/or its treatment [30]. Fatigue is multifactorial and can be influenced by social [7,31], medical [12], psychosocial [3], behavioural [32] and biological factors. In terms of socio-demographic factors, younger [26], unmarried patients [7,31] and those with a lower household income [31] have been reported to have a higher risk of reporting fatigue. Only age was significant among socio-demographic factors in this cohort. But old people and disadvantaged populations were not well represented in this sample.

The impact of cancer diagnosis and treatment on the development of fatigue is beyond doubt since fatigue is consistently higher among BC survivors than among their counterparts [26,31]. However, the mechanisms which mediate the appearance of fatigue have not been completely elucidated. In line with

other studies, the longer the time elapsed from the diagnosis the less the fatigue reported by cancer survivors. Contrary to the expected, the role of chemotherapy and radiotherapy is controversial [15,26]. In this cohort, having been exposed to chemotherapy and specifically to anthracyclines or radiotherapy was not associated with fatigue. Neither was it, having been treated with hormonal therapy. Nevertheless, larger studies [12,31] and meta-analyses [7] have found an association with chemotherapy and radiotherapy. With regards to the finding that suggests a link between trastuzumab and CRF, there are few studies examining that association, rendering conflicting results [7,33]. Unexpectedly, we found a strong relationship that could not be explained by abnormal LVEF (mean value 62%) or because of concurrent concomitant treatment. Given the small number of patients receiving trastuzumab and the aforementioned conflicting results in the literature, this hypothesis should be confirmed.

Health-related quality of life (HRQOL) is a multidimensional concept encompassing physical, psychological, existential and functional aspects. Lower scores of HRQOL are found among people with fatigue. We confirmed the association identified by Abrahams [17] with all the EORTC QLQ-C30 functional scales (physical, role, social and cognitive functioning). Interestingly, several years post-treatment, constipation, diarrhea, appetite loss, and nausea, which represent typical side effects during cancer treatment, were more frequent in survivors with persistent fatigue. This finding had already been reported in other studies [34]. Dyspnea has multiple causes including psychosocial factors. The observed associations between fatigue and dyspnea inspire about potential causal links and pathways of dyspnea and fatigue. Also fatigue and depressive symptoms go commonly together. That association of fatigue and depression is complex since fatigue can be a symptom of depression but fatigue can also precipitate depressed mood. Moreover, pretreatment levels of fatigue, anxiety or depression seem to predict post-treatment fatigue suggesting that biological, psychological or behavioural dysregulation was present before treatment [35]. However, treatment strategies might only be effective for one of the two symptoms, supporting the idea that they are distinct.

Establishing an association between physical condition and fatigue was one of most important objectives in the initial design of this prospective study. Our hypothesis consisted of assuming that more aggressive, more cardiotoxic therapies, being less active and having a poorer cardiorespiratory fitness would make up the perfect scenario for developing fatigue. Physical condition of the patient was therefore, evaluated. Physical condition is composed of a) body composition, estimated by BMI, waist and hip perimeter; b) muscular strength estimated through the test sit to stand and handgrip strength; c) cardiorespiratory fitness estimated through the MWT. BMI has consistently been associated with CRF [16,26]. Weight, BMI and hip perimeter were predictors of fatigue in this cohort. This finding, that is in line with previous reports, is interesting because contrary to other correlates, it is a modifiable feature. Contrary to our hypothesis we could not describe a significant association between the estimated VO_{2MAX} and CRF, though there was a trend towards a negative association. In fact, the gait speed which is an important part of the formula used to calculate VO_{2MAX} was associated with fatigue. The key to justify this discrepancy could be the final heart rate which is used in the formula and it is the only “heart rate” measure which does not correlate with fatigue in our sample. However, the fact that fatigue was not

associated either with muscular strength confirms that in our sample, non-anthropometric indicators of physical condition were not related to CRF. Cardiorespiratory condition has been theoretically proposed as a cause of fatigue [34] but has not been extensively studied in this setting [19]. It should be noted that estimated cardiorespiratory condition in this cohort was in the range of normative values (27.0-31.4 ml/kg/min for healthy women from 50 to 59 yo).

The strong association between heart rate and fatigue unveils a very interesting physiopathological explanation. Heart rate variability (HRV) gathers many of the factors that are discussed in the literature as involved in fatigue. Thus, diagnosis and treatment of BC is associated with therapy-induced cardiovascular injury and lifestyle perturbations, leading to increased activation of the sympathetic nervous system and decreased activation of the parasympathetic nervous system. This autonomic imbalance stimulates the hypothalamic-pituitary-adrenal-axis, the renin-angiotensin-aldosterone system and the endocannabinoid system leading to increased oxidative stress and increased inflammation [36]. Some studies had previously shown that BC survivors with cancer related fatigue have reduced HRV and elevated norepinephrine levels.[37] suggesting an autonomic dysregulation. HRV is a marker of autonomic dysfunction and its simplest measure is heart rate (HR) (and also, recovery heart rate), being the gold standard the interval R-R measured through EKG and Holter [38]. HRV has been linked to a variety of psychological and physical illnesses including all-cause mortality. Resting heart rate itself is associated with increased risk of all-cause mortality in the general population and all-cause mortality and breast cancer-specific mortality in patients with breast cancer [39].

PA is one of the few strategies which have been proved helpful for ameliorating CRF. It is disconcerting that objectively measured weekly PA was not related to fatigue scores. Neither was it when exploring vigorous PA or sedentary time. PA is closely related to physical condition and heart rate variability. Some authors attribute the benefits of the exercise to some kind of attention or the benefits of self-management [40] more than to the physical training itself. An important fact that could explain our results is that our population is widely active. Canadian researchers also reported lack of association between PA and fatigue for active BC survivors (more than 181 min/wk) [41]. It is especially interesting how this association differs when PA is subjectively evaluated. Other authors had previously reported an association of fatigue and subjective but not objective impairments[14].

Another unexpected interesting finding was the association of a higher nut intake with lower scores of fatigue. The association between fatigue and diet has been previously explored without consistent results [42]. Nuts are good sources of unsaturated fatty acids, but also protein, fiber, potassium, magnesium and vitamin E and have been associated with cancer and all-cause mortality[43]. Omega-3 fatty acids (FA) like eicosapentanoic and docosahexaenoic acids are considered anti-inflammatory whereas omega-6 FA have pro-inflammatory properties. Thus, increased intake of omega-3 relative to omega-6 was associated with reduced inflammation in an observational analysis in breast cancer survivors[44]. However, a randomized clinical trial failed to demonstrate a benefit in fatigue in BCS, with higher intake of omega-3 FA [45]. A post-hoc analysis in our sample showed an intriguing association between nut intake and indicators of HRV (basal and recovery HR).

In conclusion, a high prevalence of CRF interfering QoL in a population of mid-term BC survivors was found. Younger and obese BC survivors seem to be prone to suffer fatigue but previous cancer therapies do not justify it completely. Though CRF was strongly correlated with emotional distress, some objective correlated findings such as markers of adiposity and a higher heart rate among fatigued women would confirm a physiological substrate beyond the psychological predisposition. A deeper insight in heart rate variability and inflammatory mechanisms is warranted. The association of CRF with trastuzumab and (low) intake of nuts should be confirmed by further studies. Increasing awareness of health practitioners about the importance of assessing CRF is crucial. On the other hand, longitudinal studies are necessary to confirm the predisposing, trigger and perpetuating factors.

Strengths: Different and consistent measures of fatigue, objective evaluation of PA and objective evaluation of physical performance and anthropometry. The clinical data are obtained from the clinical records and therefore are not self-reported.

Limitations: The study was conducted in a single hospital and the sample corresponded to a well off, educated and active population and consequently results cannot be generalized. Some other limitations are: absence of the psychologist perspective in the design, lack of a healthy control, lack of information about pretreatment levels of fatigue, anxiety depression and about coping strategies. The results would have been enriched with some information about sleep patterns, cognitive dysfunction and social support.

Declarations

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Conflicts of interest: Authors state that they have no conflict of interest.

Ethics approval: Procedures in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate: Informed consent was obtained from all individual participants.

Consent for publication: N/A

Availability of data and material: The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Code availability: N/A

Authors' contributions: AAB, MRE, PO and JR participated to collecting and managing data; CFL analysed the accelerometry data; HC performed the data analysis management; ARC conceived this research and

designed experiments, data collection and recruitment. ARC wrote the article; BC, MM and CM participated in the recruitment of patients and obtaining informed consent; ARC, BC, MM, SM, MM, CGP and CM revised clinical data of patients; CGP, MM, SM handled biological samples. All authors participated in the interpretation of the results and revisions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Descriptive data

	PH-UEM-02 (n=107) Mean (SD)	PH-UEM-05 (n=73) Mean (SD)	TOTAL (n= 180) Mean (SD)
Age	51 (9)	51 (8)	51 (9)
Time from diagnosis (days)	771 (2256)	962 (632)	856 (1950)
ANTHROPOMETRY			
Height (m)	1.60 (0.06)	1.60 (0.07)	1.60 (0.06)
Weight (kg)	68 (12)	68 (11)	68 (12)
BMI (kg/m^2)	26 (4.3)	26 (4.5)	26 (4.4)
Waist (cm)	85.0 (11)	85 (11)	85 (11)
Hip (cm)	103.0 (10)	103 (9.1)	103 (9.7)
Waist to hip	0.83 (0.07)	0.82 (0.07)	0.83 (0.07)
TUMOR			
Left side	58%	54%	56%
Stage I	32%	40%	35%
Stage II	52%	44%	49%
Stage III	16%	16%	16%
TREATMENT			
Chemotherapy	–	73%	73%
Anthracyclines	72%	62%	68%
Trastuzumab	19%	22%	20%
Radiotherapy	67%	62%	65%
Hormonotherapy	77%	84%	81%
Aromatase inhibitors	–	25%	25%
PHYSICAL CONDITION			
Estimated VO_{2max} (ml/kg/min)	28 (8.5)	28 (8.0)	28 (8.3)
One mile walk test time (min)	17 (1.8)	16 (1.7)	17 (1.8)
Basal heart rate (beats/min)	75 (11)	76 (12)	75 (11)
Final heart rate (beats/min)	111 (20)	126 (17)	117(20)

Recovery heart rate (beats/min)	94 (16)	109(21)	100 (20)
Sit to stand test (s)	7.1 (2.4)	6.0 (2.4)	6.7 (2.5)
Handgrip (kg)	26 (5)	24 (5)	25 (5)
OBJECTIVELY MEASURED PHYSICAL ACTIVITY			
MVPA (min/week)	250 (183)	275 (218)	259 (197)
VPA (min/week)	4.1 (13)	7.7 (27.8)	5.5 (20)
Sedentary time (min/week)	3300 (1432)	3292 (1653)	3297 (1517)
SOCIO-DEMO (self-reported)			
Smoker	14%	8%	11%
Married/partner	75%	85%	80%
Cars	-	1.7 (0.7)	1.7 (0.7)
Square meters	-	2.5 (0.6)	2.5 (0.6)
Annual income	2.3 (0.7)	2.7 (0.7)	2.0 (0.7)
<10000€			21.7%
10-30000€			53.0%
30-60000€			24.1%
>60000€			1.2%
Education			
-Primary or less	15 %	10%	13%
-Secondary	40 %	29%	35%
- College	45 %	61%	52%
Employment status			
-Active	37%	21%	28
-Inactive	63%	79%	72
Children under 15	43%	40%	42
Disabled	3.8%	4.8%	4.3%
Health perceived			
-Very good	13.5%	10.8%	12.3%
-Good	47.1%	59.0%	52.4%

-Fair	34.6%	27.7%	31.5%
-Poor	4.8%	2.4%	3.7%
ADHERENCE TO MEDITERRANEAN DIET			
PREDIMED	8.8 (1.9)	9.4 (2.3)	9.1 (2,1)
1 (olive oil-main fat)	100%	97%	99%
2 (olive oil-quantity)	63%	66%	64%
3 (vegetables ≥ 2)	52%	74%	62%
4 (fruits ≥ 3)	49%	63%	56%
5 (red meat <1)	83%	78%	81%
6 (butter)	86%	86%	86%
7 (carbonated beverages <1)	84%	84%	84%
8 (wine ≥ 7)	14%	23%	19%
9 (pulses ≥ 3)	17%	29%	22%
10 (fish/seafood ≥ 3)	54%	59%	56%
11 (commercial pastry < 2)	54%	64%	59%
12 (nuts)	57%	51%	54%
13 (white over red meat)	9%	85%	88%
14 (mediterranean tomato sauce)	76%	81%	78%
EORTC QLQ-C30			
Functional scales			
Physical	88 (15)	72 (36)	74 (35)
Role	92 (21)	70 (39)	73 (38)
Emotional	76 (24)	61 (38)	63 (37)
Cognitive	71 (36)	63 (38)	64 (38)
Social	76 (27)	62 (39)	64 (38)
Symptom scales			
Nausea	6 (13)	2 (7)	2 (8)
Pain	21 (23)	20 (33)	20 (31)
Dyspnoea	22 (30)	12 (22)	14 (23)

Insomnia	47 (39)	37 (35)	36 (36)
Appetite loss	3 (9.6)	6 (15)	6 (15)
Constipation	25 (38)	14 (26)	14 (27)
Diarrhea	8 (15)	3 (12)	3 (11)
Financial difficulties	22 (33)	17 (30)	17 (30)
Global QOL score	72 (22)	68 (20)	69 (20)
EORTC QLQ-BR23	0.12 (0.33)	0.1 (0.33)	0.1 (0.3)
Functional scales			
Body image	83 (24)	60 (40)	62 (40)
Sexual functioning	58 (15)	59 (34)	58 (33)
Sexual enjoyment	44 (25)	25 (29)	26 (30)
Future perspective	38 (38)	41 (37)	39 (37)
Symptom scales			
Systemic side effects	24 (19)	17 (15)	18 (16)
Breast symptoms	31 (25)	17 (20)	19 (21)
Arm symptoms	20 (16)	17 (24)	17 (22)
Hair loss	13 (26)	7 (21)	8 (22)
IPAQ (self-reported)			
IPAQ			
IPAQ S	1793 (1090)	547 (774)	1276(1148)
IPAQ L	710 (958)	826 (1188)	758 (1058)
IPAQ M	326 (702)	228 (502)	286 (628)
IPAQ V	76 (151)	144 (427)	104 (297)
FATIGUE			
PERFORM SCORE	45 (12)	47 (12)	46 (12)
FACIT SCORE	-	39 (9)	39 (9)
FatigueC30 (EORTC)	22 (24)	22 (25)	22 (24)

Square meters: 1) >72; 2) 72-104; 3) >104.

Health perceived: 1) Very good; 2) Good; 3) Fair; 4) Poor; 5) Very poor.

MVPA: Moderate and vigorous physical activity; VPA: Vigorous physical activity.

Adherence to Mediterranean diet (PREDIMED score): 1 (<5) poor; 2(5-7) low; 3 (8-11) medium; 4 (12-14) high

3) How many vegetables servings do you consume per day? (2 or more) 4) How many fruit units do you consume per day) (3 or more); 5) How many servings of red meat, hamburger or meat products do you consume per day? (less than one); 6 How many servings of butter, margarine or cream do you consume per day (less than one); 7) How many carbonated and/or sugar-sweetened beverages do you consume per day? (less than one); 8) How much wine do you consume per week (more than 7 cups); 9) How many servings of pulses do you consume per week? (3 or more); 10) How many servings of fish/seafood do you consume per week? (3 or more) 11) How many times do you consume commercial pastry? (less than 2); 12) How many times do you consume nuts per week (3 or more); 13) Do you prefer to eat chicken, turkey or rabbit? (yes); 14) How many times do you consume a sauce of garlic, onion and tomato sauted in olive oil? (2 or more)

EORTC QLQ C30: The European Organization for Research and Treatment of Cancer general questionnaire

EORTC BR-23: The European Organization for Research and Treatment of Cancer specific questionnaire for breast cancer.

IPAQ: International Physical Activity Questionnaire; IPAQ S sedentary; IPAQ L low; IPAQ M moderate; IPAQ V vigorous

Table 2. Regression results of patient-reported assessments

	Coefficient	SE	p-value
SOCIODEMOGRAPHIC QUESTIONNAIRE			
Smoking	-0.42	2.73	0.878
Partner	-0.18	2.18	0.933
Economic			
Cars			
1	7.18	6.41	0.266
2	3.14	6.00	0.603
>2	6.03	7.18	0.404
House			
72-104 sm	6.42	6.12	0.299
> 104 sm	2.02	5.95	0.735
Annual income			
10000-30000€	2.41	3.59	0.505
30001-60000€	5.98	4.12	0.151
>60000€	-6.78	11.80	0.567
Education			
Secondary	-0.07	3.03	0.983
College	2.09	2.92	0.476
Employment			
Active	-2.43	2.00	0.253
Children under 15	-0.95	1.80	1.809
Disabled	-5.70	4.51	0.209
Health perceived			
Good	-6.10	2.25	0.007*
Fair	-18.86	2.39	<0.001*
Poor	-12.97	4.14	0.002*
EORTC QLQ C30			
Physical	0.16	0.04	<0.001*

Role	0.19	0.03	<0.001*
Emotional	0.17	0.03	<0.001*
Cognitive	0.16	0.03	<0.001*
Social	0.17	0.03	<0.001*
Nausea	-0.47	0.15	0.003*
Pain	-0.22	0.05	<0.001*
Dyspnoea	-0.20	0.05	<0.001*
Insomnia	-0.06	0.04	0.111
Appetite loss	-0.32	0.81	<0.001*
Constipation	-0.08	0.50	0.084
Diarrhea	-0.63	0.12	0.602
Financial difficulties	-0.17	0.04	<0.001*
EORTC BR-23			
Body image	0.16	0.31	<0.001*
Sexual functioning	-0.00	0.04	0.994
Sexual enjoyment	0.02	0.05	0.631
Future perspectives	0.10	0.03	0.003*
Systemic side effects	-0.29	0.08	<0.001*
Breast symptoms	-0.14	0.06	0.028*
Arm symptoms	-0.16	0.05	0.006*
Hair loss	-0.18	0.05	0.001*
IPAQ			
IPAQ Vigorous	0.00	0.00	0.09
IPAQ Moderate	0.00	0.00	0.09
IPAQ Light	0.00	0.00	0.03*
IPAQ Sedentary	-0.00	0.00	0.06
PREDIMED			
1	10.35	8.61	0.231
2	2.69	2.07	0.196

3	1.65	2.04	0.421
4	3.42	1.99	0.087
5	-3.36	2.50	0.181
6	3.77	2.79	0.179
7	2.43	2.75	0.377
8	0.75	2.55	0.768
9	-2.28	2.45	0.352
10	0.80	2.02	0.691
11	-2.13	2.02	0.291
12	4.88	1.96	0.014*
13	1.53	3.13	0.625
14	3.77	2.41	0.119

SE: standard errors.

PQ: Performance Questionnaire. Lower PQ scores correspond to worse fatigue. Negative sign means positive association with fatigue.

EORTC QLQ C30: The European Organization for Research and Treatment of Cancer general questionnaire.

EORTC BR-23: The European Organization for Research and Treatment of Cancer specific questionnaire for breast cancer.

3) How many vegetables servings do you consume per day? (2 or more) 4) How many fruit units do you consume per day) (3 or more); 5) How many servings of red meat, hamburger or meat products do you consume per day? (less than one); 6 How many servings of butter, margarine or cream do you consume per day (less than one); 7) How many carbonated and/or sugar-sweetened beverages do you consume per day? (less than one); 8) How much wine do you consume per week (more than 7 cups); 9) How many servings of pulses do you consume per week? (3 or more); 10) How many servings of fish/seafood do you consume per week? (3 or more) 11) How many times do you consume commercial pastry? (less than 2); 12) How many times do you consume nuts per week (3 or more); 13) Do you prefer to eat chicken, turkey or rabbit? (yes); 14) How many times do you consume a sauce of garlic, onion and tomato sauted in olive oil? (2 or more).

Table 3. Regression results of clinical data and fatigue (PQ)

	Coefficient	SE	p-value
Age	0.21	0.10	0.038*
ANTHROPOMETRIC DATA			
Height	-20.6	14.4	0.155
Weight	-0.21	0.07	0.006*
BMI	-0.42	0.20	0.042*
Waist	-0.14	0.08	0.084
Hip	-0.18	0.09	0.047*
Waist to hip	-7.69	13.81	0.579
TUMOUR AND TREATMENT DATA			
Tumour side	0.38	1.92	0.842
Time from diagnosis			
2nd Q	2.97	2.60	0.254
3rd Q	7.12	2.66	0.008*
4th Q	4.65	2.71	0.088
Stage			
II	1.58	2.02	0.433
III	-0.03	2.77	0.990
Treatment			
Chemotherapy	-3.59	3.22	0.268
Anthracyclines	-0.45	1.96	0.816
Trastuzumab	-6.00	2.28	0.009*
Hormone	2.09	2.68	0.435
Aromatase Inh	1.82	3.30	0.582
Radiotherapy	-0.15	1.93	0.936

SE (standard errors). Q (quartil). PQ: PERFORM Questionnaire.

*: p-value <0.05

Lower PQ scores correspond to worse fatigue.

Negative sign means positive association with fatigue.

Table 4. Physical condition and objectively assessed physical activity.

Regression results

	Coefficient	SE	p-value
PHYSICAL CONDITION			
Estimated VO_{2max}	0.20	0.11	0.070
Mile time	-1.06	0.49	0.036*
Basal heart rate	-0.21	0.07	0.006*
Final heart rate	-0.04	0.04	0.406
Recovery heart rate	-0.10	0.04	0.002*
Sit to stand	-0.18	0.36	0.615
Handgrip strength	-0.08	0.18	0.652
ACCELEROMETRY			
MVPA	0.0044	0.00	0.354
Sedentary	0.007	0.00	0.282
Vigorous	0.0614	0.04	0.180

*: p-value <0.05

SE: standard errors.

MVPA: Moderate and Vigorous Physical Activity.

Supplementary Files

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- Figure1.png