**Title page**

***Title***

TIME COURSE AND PREDICTORS OF PERSISTENT CANCER-RELATED FATIGUE IN LONG-TERM BREAST CANCER SURVIVORS: A PROSPECTIVE OBSERVATIONAL STUDY.

***Short running title***

*IMPACT OF PERSISTENT CANCER-RELATED FATIGUE IN LONG-TERM BREAST CANCER SURVIVORS*

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**Consent to participate:** *"Participants were welcomed for assessments by a physiotherapist, who gave detailed information about the study. Once they signed written informed consent, the researcher carried out the first assessment".*

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**Abstract**

***Purpose:*** The present study investigated whether the level of cancer-related fatigue (CRF) after finishing oncology treatment was related to higher levels of persistent CRF and its relationship with both functional and psychological disturbances. Second, to identify potential predictors of persistent CRF.

***Methods:*** Eighty BC survivors were classified into non-fatigued (≤3.9) or fatigued (≥4), according to their Piper Fatigue Scale total score after finishing oncology treatment. Time course of fatigue and the impact on its domains, pain, mood state, perceived physical fitness, the level of physical activity and quality of life were assessed at ≥5 years.

***Results:*** Women classified as fatigued after finishing oncology treatment, had not only a higher prevalence of persistent CRF (41.2%) at the reassessment, but also greater levels of pain ($P$=.006 to .048) and mood disturbances ($P$=.007 to .015), and lower levels of physical fitness condition ($P$=.002 to .039) and quality of life ($P$<.001 to <.05) over time. Regression analyses revealed that "sadness/depression", "global health status", "physical activity level", and "type of treatment" were significant predictors of persistent CRF ($r^2$=.692).

***Conclusion:*** Higher levels of CRF implied greater levels of persistent CRF and a lower functional and psychological profile over time. 69.2% of the variability of persistent CRF was explained.

**Keywords**

Breast cancer survivors; Fatigue; Persistent cancer-related fatigue; Physical health; Pain; Rehabilitation

## Main text

### Introduction

According to the 2020 GLOBOCAN, female breast cancer (BC) has now surpassed lung cancer as the leading cause of global cancer incidence, with and estimated 2.3 million cases, representing 11.7% of all cancer cases. It is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths. Furthermore, BC accounts, among women, for 1 in 4 cancer cases and for 1 in 6 cancer deaths, ranking first for incidence in the vast majority of countries (159 – 185 countries) and for mortality (110 – 185 countries) [1]. However, although this information reveals how long-term survival rates after a diagnosis of BC are steadily rising, health care practitioners must recognize and manage in rehabilitation programs, the long-term sequelae and disabilities of the constellation of therapeutic modalities affecting this population [2-4].

In this sense, the most frequent and disabling symptom across the BC continuum is cancer-related fatigue (CRF) [5,6], which alone brings a subjective permanent sense of tiredness and/or lack of energy that is not proportionate to recent activity and interferes with common functioning [7-9]. Previous studies concluded that the majority develop severe fatigue throughout their cancer treatment, from which some recover once the treatment has finished [10,11]. However, among long-term breast cancer survivors (LTBCS), someone who remains alive ≥5 years beyond cancer diagnosis, fatigue was still reported by approximately 30-41% of them [2,9, 12,13].

Early BC survivorship appears to be affected by a number of factors, including surgery and medical treatment [14], mitochondrial damage, specific phenotypic characteristics, cortisol dysregulation [15-17], proinflammatory cytokines [18], shoulder and neck pain, depression, and decreased shoulder movement [19]. However, there are not enough prospective observational studies that clarify what causes not only the appearance but also the persistence over time. Thus far, the most frequently associated factors with persistent CRF include physical and psychological conditions mainly related to pain and depressed mood [10,13,20]. Other factors, such as sleep disturbance [9], physical inactivity [10,13] or high body mass

index [12], have also been described. Despite this evidence, there is still controversy surrounding published results with respect to demographic-, disease-, and treatment-related factors.

Interestingly, Tabrizi and Alizadeh suggested in 2017 that persistent CRF is specifically correlated with marital and educational status rather than factors linked to cancer and its treatment, such as tumour stage, or having received radiotherapy and/or chemotherapy [21]. Even, other authors have shown that persistent CRF in LTBCS was correlated with younger age or lower incomes [22]. Nevertheless, Bower et al. (2006) demonstrated that LTBCS who received both radiation and chemotherapy have a greater chance of being fatigued than women only treated with radiation [9]. Considering all this, the current understanding about the time course and correlates of persistent CRF in LTBCS is still limited because there are few studies carried out in long-term survival, and the evidence to date does not establish a clear line of explanation. For these reasons, there is still a high percentage of unexplained variability of fatigue in LTBCS [9,13].

Therefore, contributing to the identification of potential modifiable predictors that may perpetuate CRF in LTBCS is a very relevant health concern, specially, when it comes to physiotherapy rehabilitation programs. In other words, the faster we can identify which factors are perpetuating CRF and putting each of our patients at risk, the faster we can offer personalized clinical treatment since not all patients will have the same risk factors and if they do, they will not be affected with the same intensity".

Hence, the aims of the present study were to analyse whether the level of CRF after finishing oncology treatment (at first assessment) was related to higher levels of persistent CRF (at reassessment) and its relationship with both functional and psychological disturbances. Second, we aimed to identify potential predictors of persistent CRF.

Thus, it was hypothesized that persistent CRF would be higher in those patients who suffered from greater levels of CRF (at first assessment), which would be related to demographic and both treatment- and disease-related factors.

## Materials and methods

### *Design and participants*

A prospective observational study was conducted with a cohort of 80 BC survivors at the Sport and Health Joint University Institute (iMUDS) in Granada. Participants were recruited through the oncology service at the University Hospital Complex of Granada. To be eligible, BC survivors had to be above the age of 18, been diagnosed with stage I-IIIa BC, and finished oncology treatment. Exclusion criteria included patients with relapsed breast cancer/other types of cancer, undergoing adjuvant hormone therapy at the time of the evaluation, having brain metastasis or any other medical or surgical central nervous system diseases that could impair their ability to complete the questionnaires or be evaluated clinically.

Participants were welcomed for assessments by a physiotherapist, who gave detailed information about the study. Once they signed written informed consent, the researcher carried out the first assessment between September 2009 and March 2012, which consisted solely of assessing the level of cancer-related fatigue. Therefore, considering published clinically significant fatigue criteria [23-25], BC survivors were allocated into two groups: non-fatigued (≤3.9) or fatigued (≥4) according to their total fatigue score on the Piper Fatigue Scale (PFS) after finishing oncology treatment. Hereinafter, between January and April 2018, the participants were again contacted for a reassessment (at least ≥ 5 years beyond every patient cancer diagnosis). Both assessments lasted approximately 1 hour. The flow diagram for study participants is presented in Figure 1.

***[Figure 1 near here]***

This study was performed in the line with the principles of The Declaration of Helsinki. Approval was granted by the Biomedical Research Ethical Committee of Granada (CEIm) (1038-N-16 I.P).

***Variables***

Fatigue was assessed at both time points, while the rest of the variables were only evaluated at the reassessment.

*Fatigue and its domains*

The Spanish version of the PFS was used, which has shown high reliability (Cronbach's α .86) in BC survivors [26]. It is composed by 22 items divided into four subscales. Each item was scored individually from 0 to 10 and then added together and divided by 22 to obtain a total fatigue score.

*Pain measures*

The Visual Analogue Scale (VAS) was used, which showed good reliability with an intraclass correlation coefficient (ICC) of .97 [27]. Participants had to mark on a horizontal line (10 cm in length) their current subjective pain intensity for both arms. Furthermore, the Spanish version of the Brief Pain Inventory (BPI) short form (Cronbach's alpha ranged between .87 and .89) [28] was also used to assess, regarding previous 24 hours, the severity of pain (pain intensity) through 4 items and its impact on daily functioning (pain interference) through 7 items, apart from a front and back body diagram. Both pain intensity and interference are obtained from mean scores.

*Mood measures*

The Scale for Mood Assessment (EVEA) was used, whose 16 Likert-scales are divided into 4 categories and have shown good reliability (Cronbach's alpha ranged between .88 and .93) [29].

*Fitness condition*

The Spanish version of the International Fitness Scale (IFIS), which measures general physical fitness along with cardiorespiratory fitness, muscular strength, speed/agility, and flexibility in comparison to a friend's level of physical fitness. It is scored using a Likert scale with a maximum of five response possibilities: very poor, poor, average, good, and very good. The reliability of this test was Cronbach's alpha .80 [30].

*Physical activity level*

The Minnesota Leisure Time Physical Activity (MLTPA) questionnaire was also used, which has shown good reliability with an ICC of .84 [31,32]. Participants marked how many times each physical activity (PA) was performed during the last week and the average of hours expended for each one. Furthermore, a metabolic equivalent task (MET) of 1 kcal/min was multiplied by the time reported for each PA to calculate energy expenditure [33].

*Quality of life measures*

The EORTC QLQ-C30 version 3.0 and its BC module EORTC-BR23 were used to assess quality of life (QoL) through several scales divided into 5 functioning scales, 3 symptom scales, 6 single items, and a global health status scale for the QLQ-C30 and both 4 functioning and 4 symptom scales for the QLQ-BR23. Both instruments have shown adequate reliability (Cronbach's alpha ranged between .46 and .94) [34,35].

***Statistical analyses***

The homogeneity between groups in sociodemographic and medical characteristics using *t* tests for continuous variables and chi-square tests for categorical variables, was summarized and compared.

The Kolmogorov-Smirnov test was used to check normality in the distribution of the data (P>.05). The intra-group differences for times courses of fatigue at both post oncology treatment and at ≥5 years with analyses of variance (ANOVA) was also analysed. Furthermore, the differences between groups using ANOVA, with non-fatigue or fatigue after finishing oncology treatment as the independent variable, and fatigue domains, pain, mood parameters, physical fitness, the level of leisure time PA, and QoL at ≥5 years as dependent variables, were analysed. Mann-Whitney U test were used when data have non-normal distribution.

Pearson's correlation analysis was carried out between the persistent CRF using the value acquired for the "PFS Total Score" at ≥5 years in the fatigued group and the other study variables. Stepwise multiple regression analysis was also used to explore which variables could explain the variation in persistent CRF. The requirements for an independent variable to be included in the multiple regression analysis were as follows: 1) the correlation coefficients between the dependent variable and the independent variables were significant; and 2) the correlation coefficients between the independent variables <.70 to avoid collinearity occurrence [36].

Since the significant predictors should be individually and sequentially entered into the regression model according to their relationship with the dependent variable, we used the forward selection procedure to analyze the data. The significance level of the linear regression results was tested at each step, and the standardized $\beta$ coefficients for each variable in the final model were calculated.

## Results

Of the 149 BC survivors recruited, 46.31% (n=69) of them were not in attendance for the first assessment, and, consequently, neither to the second for the following reasons: declined to participate 8.39% (n=12), living far away 15.44% (n=23), busy 9.39% (n=14), health 3.36% (n=5), and other reasons

9.73% (n=15). However, none of the 80 patients were lost at follow-up between the first and the second assessment (see Figure 1).

***Characteristics measure scores***

No differences were found between groups after the end of oncology treatment considering fatigue criteria [23-25]. In the fatigued group, the mean age was 48.96±8.00 years old, while in the non-fatigued group was 49.88±8.62 years old. With respect to the fatigued group, 52.7% had stage 2 of BC and 89.1% received both radiotherapy and chemotherapy, whilst 56% had stage 2 of BC in the non-fatigued group, and 88% received both radiotherapy and chemotherapy. The overall data about the characteristics measure scores are reported in Table 1.

***[Table 1 near here]***

***Time courses of fatigue***

The fatigued group (n=55, 68.75%) had higher levels of CRF (6.23±1.42) after finishing oncology treatment (at first assessment) and reported higher significant levels of persistent CRF (4.20±2.92) over time (at reassessment) compared with the non-fatigued group (n=25, 31.25%), who had a level of CRF of 2.26±1.37 at first assessment and a level of persistent CRF at reassessment of 1.95±2.11 (see Figure 2). Interestingly, it is also worth noting that the percentage of fatigued women at first evaluation was 68.75% (n=55) and 41.25% (n=33) at reassessment. As for the other group, it can be highlighted how the percentage of non-fatigued women during the first evaluation was 31.25% (n=25) and 58.75% (n=47) at reassessment. Finally, 27.5% (n=22) of the patients did not present fatigue in either of the two evaluations, 41.25% (n=33) had fatigue in the first evaluation but stopped being fatigued at the reassessment and 31.25% (n=25) presented fatigue in both evaluations.

***[Figure 2 near here – Supplemental material]***

***Fatigue Domains***

The ANOVA found significant differences between groups in the PFS domains. The fatigued group, who reported higher levels of CRF after finishing oncology treatment, also showed significant higher levels of "behavioural/severity" (F=3.18; P=.024), "affective" (F=10.30; P=.001), "sensory" (F=2.68; P=.009), and "cognitive/mood" (F=3.53; P=.018) persistent CRF than the non-fatigued group over time (see Figure 3).

*[Figure 3 near here – Supplemental material]*

***Pain, mood state, physical fitness and physical activity level***

The ANOVA found significant differences between groups in the VAS and BPI. The fatigued group, who had greater levels of CRF after finishing oncology treatment, exhibited more pain in the "non-affected arm" (F=10.07; P=.048) and more "pain intensity" (F=8.50; P=.015) and "pain interference" (F=19.43; P=.006) than the other group at the reassessment. No significant differences between groups in the "affected arm" (P>.05) were observed. The overall data about pain, mood state, physical fitness and physical activity level are reported in Table 2.

*[Table 2 near here]*

The ANOVA also found that the EVEA was significantly different between groups. The fatigued group, who reported greater levels of CRF after finishing oncology treatment, displayed higher levels of "sadness/depression" (F=5.31; P=.015), "anxiety" (F=29.51; P=.007), and "anger/hostility" (F=21.69; P=.009) than the non-fatigued group at the reassessment. There were no significant differences for "happiness" between groups (P>.05) (see Table 2).

The ANOVA revealed that all the IFIS domains were significantly different between groups except for "muscular strength" (P>.05). The non-fatigued group, who reported inferior levels of CRF after finishing oncology treatment, identified themselves with higher levels of "general physical fitness" (F=1.30; P=.032), "cardiorespiratory fitness" (F=.25; P=.002), "speed/agility" (F=.02; P=.039), and "flexibility" (F=3.88; P=.033) than the other group at the reassessment. Nonetheless, no significant differences between groups in the MLTPA questionnaire were found (P>.05) (see Table 2).

***Quality of life***

The ANOVA showed that the QLQ-C30 were significantly different between groups: "Physical" (U= 459.50), "role" (F=13.55), "emotional" (F=8.36), "cognitive" (F=5.89), and "social" (F=9.58) functioning, as well as "global health status" (F=2.51) were greater in the non-fatigued group (*P*<.001 to .028) at the reassessment. On the contrary, "fatigue", "pain", "dyspnea", and "insomnia" were higher in those who exhibited higher levels of CRF compared to the other group (F=.50 to 13.40; *P*<.001 to .006) at the reassessment. Regarding the QLQ-BR23, we found that "body image" (F=12.24; P=.019) was

significantly superior in the non-fatigued group in comparison to the other group at the reassessment. Nevertheless, “systemic therapy side effects”, “breast symptoms”, and “arm symptoms” were greater in the fatigued group (F=3.72 to 10.07; *P*<.004 to .040) at the reassessment. There were not significant differences between groups for the rest of the variables in both questionnaires (P>.05). Results are presented in Table 3.

***[Table 3 near here]***

***Correlation analyses***

Significant positive correlations between persistent CRF and the following variables: “family history of BC”, “type of treatment”, “dyspnea”, “insomnia”, “systemic therapy side effects”, “breast symptoms”, “arm symptoms”, “pain affected arm”, “sadness/depression”, “anxiety” and “anger/hostility" were found (*r*= .270 to .743; *P*<.001 to .046). While significant negative correlations between persistent CRF and the following variables: “cognitive”, and “social” functioning, “global health status”, “body image”, “future perspective”, “general physical fitness”, “PA level”, and “happiness” were observed (*r*= -.267 to -.618; *P*<.001 to .049). Results are represented in Figure 4.

***[Figure 4 near here]***

***Multiple Regression Analysis***

The final model revealed that “sadness/depression”, “global health status”, “PA level”, and “type of treatment” were significant predictors of persistent CRF, and whose interaction explained 69.2% of the persistent CRF variance ($r^2$adjusted=.692; *P*<.001) ≥5 years beyond the end of oncology treatment. Results of the multiple regression analysis are reported in Table 4.

***[Table 4 near here]***

**Discussion**

The purpose of this study was to analyse whether the level of CRF after finishing oncology treatment was related to higher levels of persistent CRF and its relationship with both functional and psychological disturbances on the one hand, and to identify potential predictors of persistent CRF on the other.

The main findings of this study showed that women classified as fatigued after finishing oncology treatment have not only a higher prevalence of persistent CRF (41.2%) at the reassessment, but also have greater levels of pain and mood disturbances and lower levels of physical fitness condition and QoL over time. Furthermore, 69.2% of the persistent CRF variance was explained by the combination of "sadness/depression", "global health status", "PA level", and "type of treatment".

Despite a clinically significant decrease in the level of fatigue over time (≥2 points difference on the PFS total score) [23], the level of persistent CRF is still moderate (≥4) in those patients who had higher levels of CRF after the end of oncology treatment [13,37,38], and what is more, 31.25% of those patients have been and continue to be permanently fatigued. Previous evidence showed discrepancies because some studies had demonstrated a lack of change in this symptom over time [5], while others have confirmed an increase [12] or even a reduction [22]. It should be stressed that the percentage of the prevalence of fatigue in the current study (41.2%) was between 15-30% above that reported by previous studies in LTBCS [5,12,22,39]. It is possible that this dissimilarity may have been caused by the use of a different instrument to assess fatigue, a different cut-off point or both. Furthermore, the majority of the survivors in the research conducted by Bower et al. (2000) received radiotherapy [22], while in our study, the majority received the combination of radiotherapy and chemotherapy, which is already known to cause higher levels of fatigue over time compared to receiving either radiotherapy or chemotherapy [9]. Additionally, all the PFS domains included in the study (i.e., "behavioural/severity", "affective", "sensory", and "cognitive/mood") were significantly higher in the fatigued group, which indicated that the four areas were affected at the reassessment by the presence of greater levels of CRF after finishing oncology treatment. Therefore, these findings confirm the main hypothesis that one of the most prevalent symptoms among BC patients is still present years after the end of oncology treatment [2,5,10,11,39], which in turn may also lead to a negative impact on their health status and QoL [40]. Because of this, and considering that a fatigue severity cut-score ≥4 on a 0-10 scale has been previously used as a cut-off score to make treatment decisions [37], surveillance and rehabilitation programmes in long-term survivorship should be implemented to detect this symptom and subsequently address and treat it in this population.

This study also explored the co-occurrence of fatigue with other disruptive symptoms (both physical and psychological). In this sense, the fatigued group exhibited significantly greater levels of spontaneous pain, “pain intensity” and “pain interference”, mood disturbances, and “symptoms severity”, along with lower levels of self-reported physical fitness condition and “functioning” compared to the other group over time. However, although these findings are consistent with those found in previous studies conducted with LTBCS suffering from high levels of fatigue [2,9,21,39-43], it is necessary to remark how these prior studies only assessed some of the variables mentioned above among their groups. Therefore, to the best of our knowledge, this is one of the few studies to explore the impact of fatigue in depth through numerous health domains in the same sample.

Conspicuously, this study further indicated that no significant differences between groups for the level of PA were found. Notwithstanding, it could be observed that many years beyond the end of cancer treatment, women from both the non-fatigued and fatigued groups were under the recommended PA minimum (600 METs min/wk), which had been previously associated with reductions in the risk of BC compared to those performing lower amounts [44]. PA also had a protective effect on CRF and its persistence [45]; therefore, the lack of PA may help perpetuate existing fatigue.

On the other hand, our results suggest that higher symptom severity, type of treatment, as well as mood disturbances seem to contribute to persistent CRF. In contrast, greater physical fitness, higher levels of happiness, and better global health status seem to have a positive impact over the persistence of this symptom over time. These findings confirm the results of previous studies that have already highlighted the impact of these factors on persistent CRF in LTBCS [11,46]. As a possible cause of these associations, recent investigations have indicated how depression and anxiety could provoke a general inflammatory state, with inflammation being involved in the aetiology of CRF [47-49]. On the contrary, PA not only reduced mood disturbances and pain but also improved confidence, self-efficacy, quality of sleep, cardiopulmonary fitness, and muscle strength, as well as increased the level of anti-inflammatory cytokines; thus, PA exerts a protective role against the disruption of CRF through a variety of mechanisms [17]. In this way, we dare speculate that this general inflammatory state, produced by several factors, such as anxiety [47], depression [47], and lack of PA [17], could not only result in the aetiology of CRF but also contribute to its persistence because these factors seemed to be still be present over time

and therefore, played an identifying role in the transition from CRF to persistent CRF, as observed among our patients.

Finally, the multiple regression analyses showed associations for some predisposing factors and persistent CRF. In this sense, higher levels of depression, poorer global health status, lower PA level, and the combination of both radiotherapy and chemotherapy seem to contribute to the variability (69.2%) of the persistence of this symptom overtime among LTBCS. Previous multiple regression analyses, such as Bower et al. (2006), indicated that predictors of persistent CRF included depression, cardiovascular problems and type of treatment received, which explained 45% of the variability [9]. Similarly, Meeske et al. (2007) concluded that 40% of the variability of persistent CRF was explained by pain, cognitive problems, physical inactivity, weight gain and antidepressant use [13]. However, the fact that our study explained between 24.2-29.2% more of the variability of persistent CRF and identified global health status as another predictor, could be a result of a different methodological approach regarding not only the use of different instruments to assess fatigue but also the inclusion and assessment of distinct dependent variables among the studies. Henceforth, given the increasing number of LTBCS, health professional should consider that not only physical and psychological factors, but also the type of treatment received, may play an important role in the persistence of this symptom, which in turn seems to negatively impact QoL. Future research should explore these findings in longer follow-up periods and stablish higher risk groups and possible preventive measures in this population, which in turn, could be extrapolated to rehabilitation programs.

The study has various limitations that merit attention. First, the value used as the cut-off point (a score of 4) to divide participants into non-fatigued or fatigued has been previously used and accepted [13,37,38], although other cut-off values could have modified our results. Second, the fact that the two fatigue assessments should be taken with caution as fatigue could not be assessed before starting oncologic treatment. Third, the high level of non-participation could have also influenced our results. Despite these cited limitations, this study incorporates a long-term assessment of persistent CRF, and the use of the PFS, which is a multidimensional instrument first validated in women with BC [23-25]. Moreover, this is one of the few studies that, through several health domains and validated and reliable instruments in cancer patients, identified potential predictors of persistent CRF, which could help to establish new approaches in the long-term rehabilitation of this growing population.

In conclusion, women classified as fatigued after finishing oncology treatment showed not only greater levels of persistent CRF at the reassessment but also a lower functional and psychological profile over time, which could subsequently have a negative impact on their QoL. Furthermore, this study allowed a better comprehension of the relationship between persistent CRF (experienced by 41.2% of women) and its possible predictors, given that "sadness/depression", "global health status", "PA level", and "type of treatment" explained 69.2% of its variability in LTBCS.

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### *Competing interests*

The authors have no relevant financial or non-financial interests to disclose.

### *Authors contribution*

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Francisco Álvarez Salvago], [José Daniel Jimenez García], [Agustín Aibar Almazán], [Fidel Hita Contreras], and [Antonio Martínez Amat]. The first draft of the manuscript was written by [Francisco Álvarez Salvago], [Jose Daniel Jimenez García], and [Agustín Aibar Almazán] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

### *Declaration of interest statement*

The authors report no conflict of interest.

**Table 1.** Demographic, medical and treatment-related characteristics after finishing oncology treatment; comparison of those who were non-fatigued and fatigued.

| Characteristics | Fatigue after finishing oncology treatment | | *P* |
|---|---|---|---|
| | Non-Fatigued (n=25) | Fatigued (n=55) | |
| **Mean Age ± SD, Years** | 49.88±8.62 | 48.96±8.00 | .171 |
| **Time Since The First Surgery, n (%)** | | | |
| 0 to 11,9 months | 14 (56) | 42 (76.36) | |
| ≥ 12 months | 11 (44) | 13 (23.64) | .065 |
| **Marital Status, n (%)** | | | |
| Unmarried | 3 (12) | 9 (16.4) | |
| Married | 19 (76) | 37 (67.3) | |
| Divorced | 0 (0) | 8 (14.5) | .060 |
| Widowed | 3 (12) | 1 (1.8) | |
| **Educational Level, n (%)** | | | |
| Primary School | 13 (52) | 21 (38.2) | |
| Secondary School | 5 (20) | 13 (23.6) | .501 |
| University | 7 (28) | 21 (38.2) | |
| **Employment Status, n (%)** | | | |
| Housewife | 11 (44) | 14 (25.5) | |
| Currently working | 6 (24) | 11 (20) | |
| Work leave | 7 (28) | 23 (41.8) | |
| Retired because of disability | 1 (4) | 7 (12.7) | .240 |
| Retired | 0 (0) | 0 (0) | |
| Unemployed | 0 (0) | 0 (0) | |
| **Tumour Stage, n (%)** | | | |
| I | 4 (16) | 18 (32.7) | |
| II | 14 (56) | 29 (52.7) | .327 |
| IIIa | 7 (28) | 8 (14.5) | |
| **Tobacco Consumption, n (%)** | | | |
| Non-smoker | 16 (64) | 22 (40) | |
| Smoker | 4 (16) | 17 (30.9) | .130 |
| Ex-smoker | 5 (20) | 16 (29.1) | |
| **Alcohol Consumption, n (%)** | | | |
| Non-consumption | 10 (40) | 19 (34.5) | |
| Monthly | 5 (20) | 15 (27.3) | .433 |
| Weekly | 10 (40) | 17 (30.9) | |

| | | | |
|---|---|---|---|
| Daily | 0 (0) | 4 (7.3) | |
| **Menopause, n (%)** | | | |
| No | 3 (12) | 7 (12.7) | |
| Yes | 22 (88) | 48 (87.3) | .927 |
| **Family History of Breast Cancer, n (%)** | | | |
| No | 12 (48) | 28 (50.9) | |
| Yes | 13 (52) | 27 (49.1) | .809 |
| **Type of treatment (%)** | | | |
| None | 0 (0) | 0 (0) | |
| Radiotherapy or Chemotherapy | 3 (12) | 6 (10.9) | .886 |
| Radiotherapy and Chemotherapy | 22 (88) | 49 (89.1) | |
| **Type of medication (%)** | | | |
| None | 5 (20) | 10 (18.2) | |
| Tamoxifen | 9 (36) | 29 (52.7) | .428 |
| Other types | 11 (44) | 16 (29.09) | |

**P<.05***

NOTE. P values for between-groups differences were calculated using the *t* test for continuous variables and $X^2$ for categorical variables.

**Abbreviations:** n: Sample size; SD: Standard deviation.

**Table 2.** Between-group differences for pain, mood state, physical fitness and leisure time physical activity values at reassessment.

| Outcomes at reassessment | Fatigue after finishing oncology treatment | | *P* | *Cohen's d* |
|---|---|---|---|---|
| | Non-fatigued (n=25) | Fatigued (n=55) | | |
| **VAS (cm), mean ± SD (95%CI)** | | | | |
| *Affected Arm* | 1.52 ± 1.96 | 2.64 ± 2.72 | .069[a] | 0.47 |
| | (95% CI .71 - 2.33) | (95% CI 1.90 - 3.37) | | |
| *Non-Affected Arm* | .64 ± 1.87 | 1.93 ± 2.94 | **.048**[a] | 0.52 |
| | (95% CI -.13 - 1.41) | (95% CI 1.13 - 2.72) | | |
| **BPI, mean ± SD (95%CI)** | | | | |
| *Intensity* | 1.28 ± 1.82 | 2.73 ± 2.64 | **.015**[a] | 0.63 |
| | (95% CI .53 - 2.03) | (95% CI 2.02 - 3.45) | | |
| *Interference* | .83 ± 1.76 | 2.57 ± 2.83 | **.006**[a] | 0.73 |
| | (95% CI .11 - 1.56) | (95% CI 1.81 - 3.34) | | |
| **EVEA, mean ± SD (95%CI)** | | | | |
| *Sadness-Depression* | 1.79 ± 2.09 | 3.37 ± 2.85 | **.015**[a] | 0.63 |
| | (95% CI .93 - 2.65) | (95% CI 2.59 - 4.16) | | |
| *Anxiety* | 1.85 ± 1.31 | 3.55 ± 2.91 | **.007**[a] | 0.75 |
| | (95% CI 1.31 - 2.39) | (95% CI 2.75 - 4.35) | | |
| *Anger / Hostility* | 1.13 ± 1.23 | 2.67 ± 2.77 | **.009**[a] | 0.71 |
| | (95% CI .62 - 1.64) | (95% CI 1.91 - 3.44) | | |
| *Happiness* | 6.02 ± 2.60 | 5.08 ± 2.29 | .111[a] | 0.38 |
| | (95% CI 4.95 - 7.09) | (95% CI 4.45 - 5.72) | | |
| **IFIS, mean ± SD (95%CI)** | | | | |
| *General Physical Fitness* | 3.64 ± .99 | 3.13 ± .96 | **.032**[a] | 0.52 |
| | (95% CI 3.23 - 4.05) | (95% CI 2.87 - 3.39) | | |
| *Cardiorespiratory Fitness* | 3.44 ± 1.12 | 2.64 ± 1.01 | **.002**[a] | 0.75 |
| | (95% CI 2.98 - 3.90) | (95% CI 2.36 - 2.91) | | |
| *Muscular Strength* | 3.16 ± 1.07 | 2.75 ± .96 | .093[a] | 0.40 |
| | (95% CI 2.72 - 3.60) | (95% CI 2.48 - 3.01) | | |
| *Speed / Agility* | 3.28 ± .94 | 2.71 ± 1.08 | **.039**[a] | 0.59 |
| | (95% CI 2.89 - 3.67) | (95% CI 2.54 - 3.06) | | |
| *Flexibility* | 3.24 ± .83 | 2.71 ± 1.08 | **.033**[a] | 0.55 |
| | (95% CI 2.90 - 3.58) | (95% CI 2.42 - 3.00) | | |

| | | | | |
|---|---|---|---|---|
| **MLTPA (MET-min/wk), mean ± SD** | | | | |
| **(95%CI)** | | | | |
| *Physical activity level* | 399.34 ± 371.36 | 421.35 ± 381.73 | .988[b] | 0.05 |
| | (95% CI 246.05 – 552.62) | (95% CI 318.15 – 524.54) | | |

**P<.05* / P<.001****

[a] Analysis of variance (ANOVA)

[b] Mann-Whitney U test

**Abbreviations:** n= Sample size, SD= Standard deviation, VAS = Visual Analogue Scale, BPI = Brief Pain Inventory, EVEA = Scale for Mood Assessment, IFIS = International Fitness Scale, MLTPA= Minnesota Leisure time physical activity questionnaire, MET-min/wk= Metabolic Equivalent of Task minutes/week, CI= Confidence Interval.

**Table 3.** Between-group differences for quality of life values at reassessment.

| Outcomes at reassessment | Fatigue after finishing oncology treatment | | *P* | *Cohen's d* |
|---|---|---|---|---|
| | Non-fatigued (n=25) | Fatigued (n=55) | | |
| **Functioning Scales QLQ-C30** | | | | |
| *Physical Functioning* | 90.17 ± 10.55 (95% CI 85.82-94.53) | 77.70 ± 22.56 (95% CI 71.60-83.80) | **.016[b]** | 0.70 |
| *Role Functioning* | 90.00 ± 15.21 (95% CI 83.72 – 96.28) | 74.55 ± 32.84 (95% CI 65.67 – 83.42) | **.028[a]** | 0.6 |
| *Emotional Functioning* | 84.33 ± 17.89 (95% CI 76.95 – 91.72) | 56.21 ± 31.48 (95% CI 47.70 – 64.72) | **<.001[a]** | 1.09 |
| *Cognitive Functioning* | 76.00 ± 22.09 (95% CI 66.88 – 85.11) | 55.45 ± 32.40 (95% CI 46.70 – 64.21) | **.005[a]** | 0.74 |
| *Social Functioning* | 89.33 ± 17.92 (95% CI 81.93 – 96.73) | 64.85 ± 34.05 (95% CI 55.64 – 74.05) | **.001[a]** | 0.89 |
| **Symptom Scales QLQ-C30** | | | | |
| *Fatigue* | 19.55 ± 19.05 (95% CI 11.69 – 27.41) | 44.24 ± 32.81 (95% CI 35.37 – 53.11) | **.001[a]** | 0.92 |
| *Nausea and vomiting* | 6.00 ± 15.87 (95% CI -.55-12.55) | 8.18 ± 19.21 (95% CI 2.99-13.38) | .653[b] | 0.12 |
| *Pain* | 18.67 ± 22.73 (95% CI 9.28 – 28.04) | 47.88 ± 31.92 (95% CI 39.25 – 56.51) | **<.001[a]** | 1.05 |
| **Single Items QLQ-C30** | | | | |
| *Dyspnea* | 9.33 ± 15.27 (95% CI 3.03 – 15.64) | 29.70 ± 34.36 (95% CI 20.41 – 38.98) | **.006[a]** | 0.76 |
| *Insomnia* | 29.33 ± 29.38 (95% CI 17.21 – 41.46) | 59.70 ± 32.03 (95% CI 51.04 – 68.36) | **<.001[a]** | 1.15 |
| *Appetite Loss* | 6.66 ± 13.61 (95% CI 1.05-12.28) | 13.94 ± 29.18 (95% CI 6.05-21.83) | .569[b] | 0.31 |
| *Constipation* | 17.33 ± 23.80 (95% CI 7.51-27.16) | 46.59 ± 136.59 (95% CI 9.30 – 83.87) | .217[b] | 0.29 |
| *Diarrhea* | 14.66 ± 23.73 (95% CI 4.87-24.46) | 28.47 ± 135.26 (95% CI -8.10-65.03) | .293[b] | 0.14 |
| *Financial Difficulties* | 17.33 ± 29.06 (95% CI 5.34-29.33) | 43.07 ± 136.04 (95% CI 6.27-79.85) | .279[b] | 0.26 |
| **Global Health Status QLQ-C30** | | | | |
| *Global Health Status* | 72.67 ± 17.60 (95% CI 65.40 – 79.93) | 60.15 ± 23.22 (95% CI 53.87 – 66.43) | **.019[a]** | 0.60 |
| **Functional Scales QLQ-BR23** | | | | |
| *Body Image* | 88.00 ± 18.01 | 72.27 ± 30.43 | **.019[a]** | 0.62 |

| | | | | |
|---|---|---|---|---|
| | (95% CI 80.56 – 95.44) | (95% CI 64.05 – 80.50) | | |
| *Sexual Functioning* | 25.00 ± 19.03 | 20.30 ± 22.15 | .369[a] | 0.22 |
| | (95% CI 16.96 – 33.04) | (95% CI 14.31 – 26.29) | | |
| *Sexual Enjoyment* | 31.75 ± 26.83 | 31.67 ± 30.15 | .992[a] | 0.02 |
| | (95% CI 19.53 – 43.96) | (95% CI 22.02 – 41.31) | | |
| *Future perspective* | 66.67 ± 30.43 | 49.40 ± 40.50 | .057[a] | 0.48 |
| | (95% CI 54.11 – 79.23) | (95% CI 38.14 – 60.04) | | |
| **Symptom Scales QLQ-BR23** | | | | |
| *Systemic Therapy Side Effects* | 18.09 ± 16.44 | 33.40 ± 23.31 | **.004[a]** | 0.75 |
| | (95% CI 11.31 – 24.88) | (95% CI 27.10 – 39.70) | | |
| *Breast Symptoms* | 16.67 ± 23.45 | 30.45 ± 28.16 | **.036[a]** | 0.53 |
| | (95% CI 6.99 – 26.35) | (95% CI 22.84 – 38.07) | | |
| *Arm Symptoms* | 21.33 ± 20.52 | 36.56 ± 33.65 | **.040[a]** | 0.54 |
| | (95% CI 12.86 – 29.80) | (95% CI 27.47 – 45.66) | | |
| *Upset by hair loss* | 21.21 ± 22.47 | 34.06 ± 32.75 | .250 | 0.45 |
| | (95% CI 6.11 – 36.31) | (95% CI 19.89 – 48.22) | | |

**P<.05* / P<.001****

[a] Analysis of variance (ANOVA)

[b] Mann-Whitney U test

**Abbreviations:** n= Sample size, SD= Standard deviation, QLQ = Quality of Life Questionnaire, CI = Confidence Interval.

**Table 4.** Summary of Stepwise Multiple Regression Analysis to determine predictors of persistent cancer-related fatigue at reassessment.

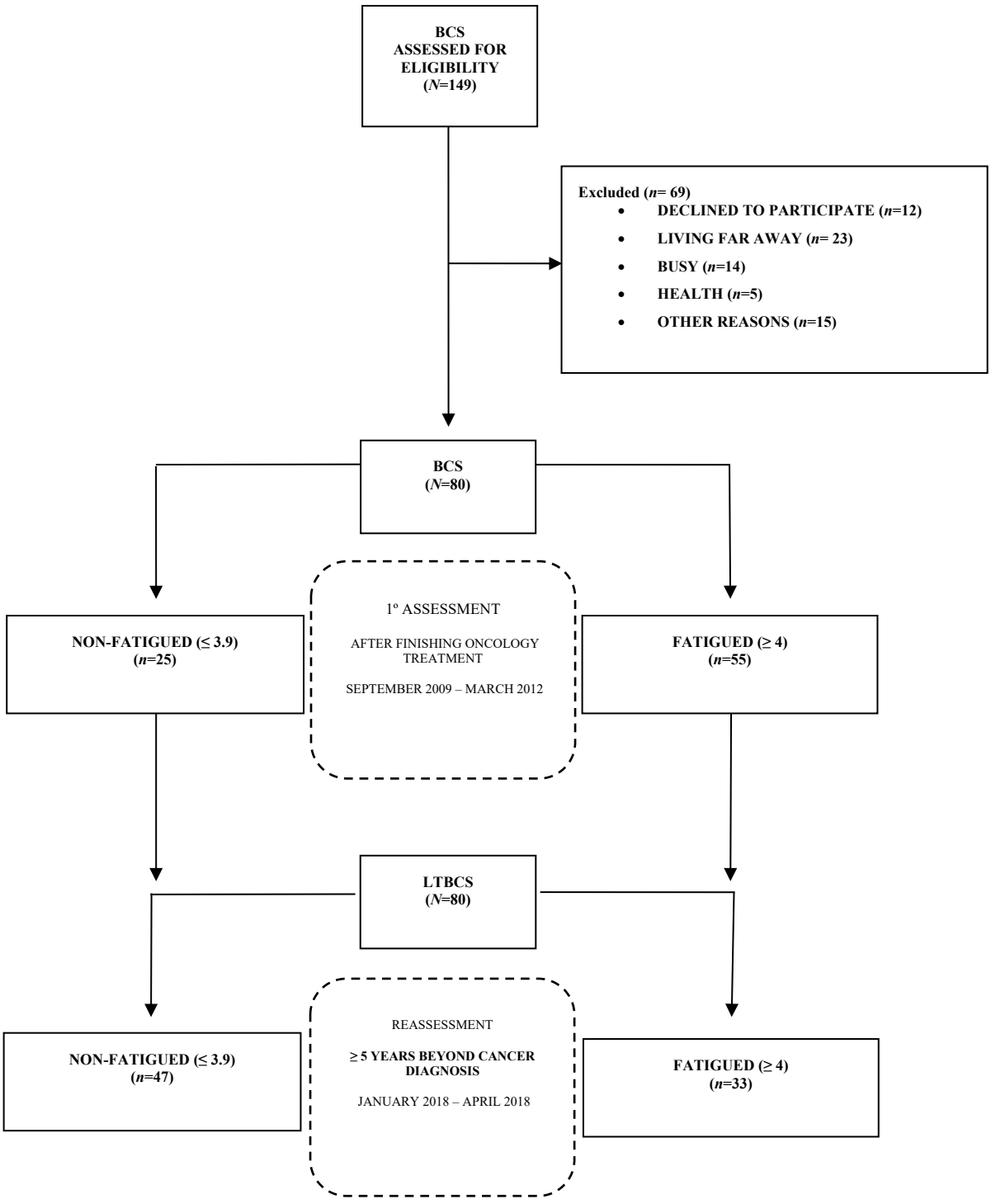
| | **Model 1** $r^2$=.554 | | | | | **Model 2** $r^2$=.612 | | | | | **Model 3** $r^2$=.651 | | | | | **Model 4** $r^2$=.692 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Outcomes at reassessment** | **β** | **95% IC** | ***t*** | ***P*** | **Linear regression equation Y= a + bX** | **β** | **95% IC** | ***t*** | ***P*** | **Linear regression equation Y= a + bX** | **β** | **95% IC** | ***t*** | ***P*** | **Linear regression equation Y= a + bX** | **β** | **95% IC** | ***t*** | ***P*** | **Linear regression equation Y= a + bX** |
| ***Sadness/ Depression*** | .743 | .571 ± .957 | 7.936 | .000 | PFTS at reassessment = 1.329 + (.764* Sadness/Depression) | .615 | .435 ± .829 | 6.439 | .000 | PFTS at reassessment = 4.101 + (.632* Sadness/Depression) + (-.039 *Global Health Status) | .555 | .377 ± .763 | 5.931 | .000 | PFTS at reassessment = 5.072 + (.570* Sadness/Depression) + (-.040 *Global Health Status) + (-.100 *PA level) | .491 | .317 ± .693 | 5.411 | .000 | PFTS at reassessment = 9.325 + (.491* Sadness/Depression) + (-.339 *Global Health Status) + (-.220* PA level) + (-.219* Type of treatment) |
| ***Global Health Status*** | | | | | | -.301 | -.064 ± -.014 | -3.154 | .003 | | -.307 | -.063 ± -.016 | -3.394 | .001 | | -.339 | -.066 ± -.021 | -3.946 | .000 | |
| ***PA level*** | | | | | | | | | | | -.219 | -.178 ± -.022 | -2.574 | .013 | | -.220 | -.174 ± -.027 | -2.756 | .008 | |
| ***Type of treatment*** | | | | | | | | | | | | | | | | -.219 | -3.474 ± -.542 | -2.754 | .008 | |

**P<.05* / P<.001****

Dependent variable: Piper Fatigue Total Score; $r^2$, Adjusted coefficient of determination; β, Regression coefficient; t, Coefficient t-value.

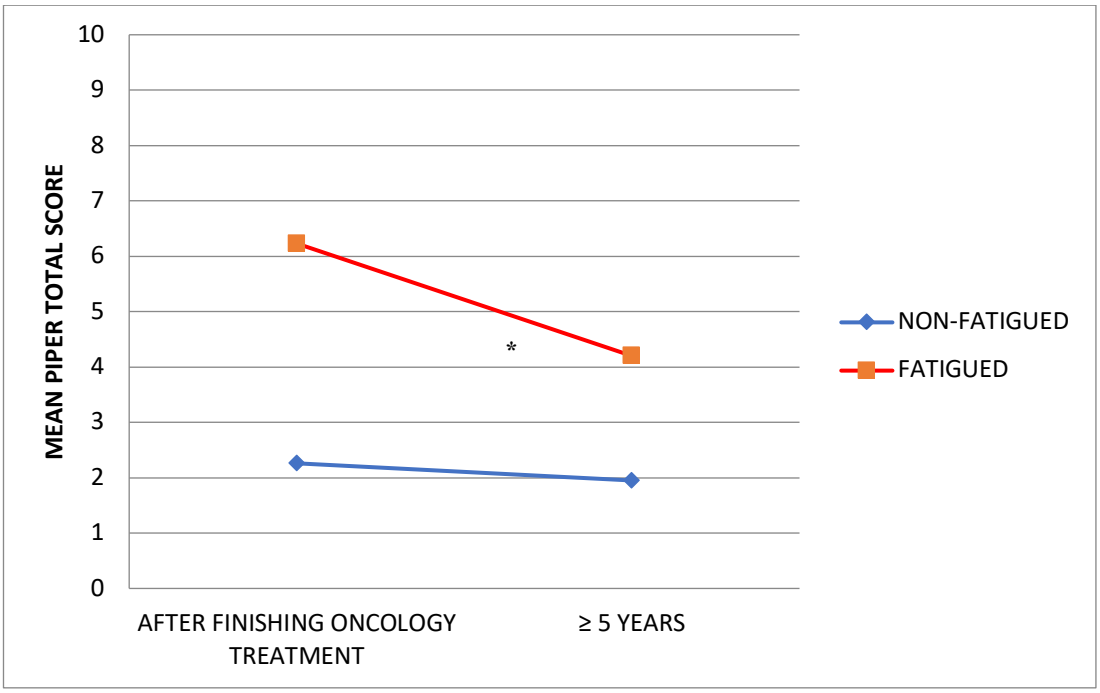
**Abbreviations:** PA= Physical activity, PFTS = Piper Fatigue Total Score, IC = Confidence Interval.

**Figure 1.** Flow diagram for study participants.




**Abbreviations:** *N*/*n:* simple size; BCS: Breast cancer survivors; LTBCS: Long-term breast cancer survivors.

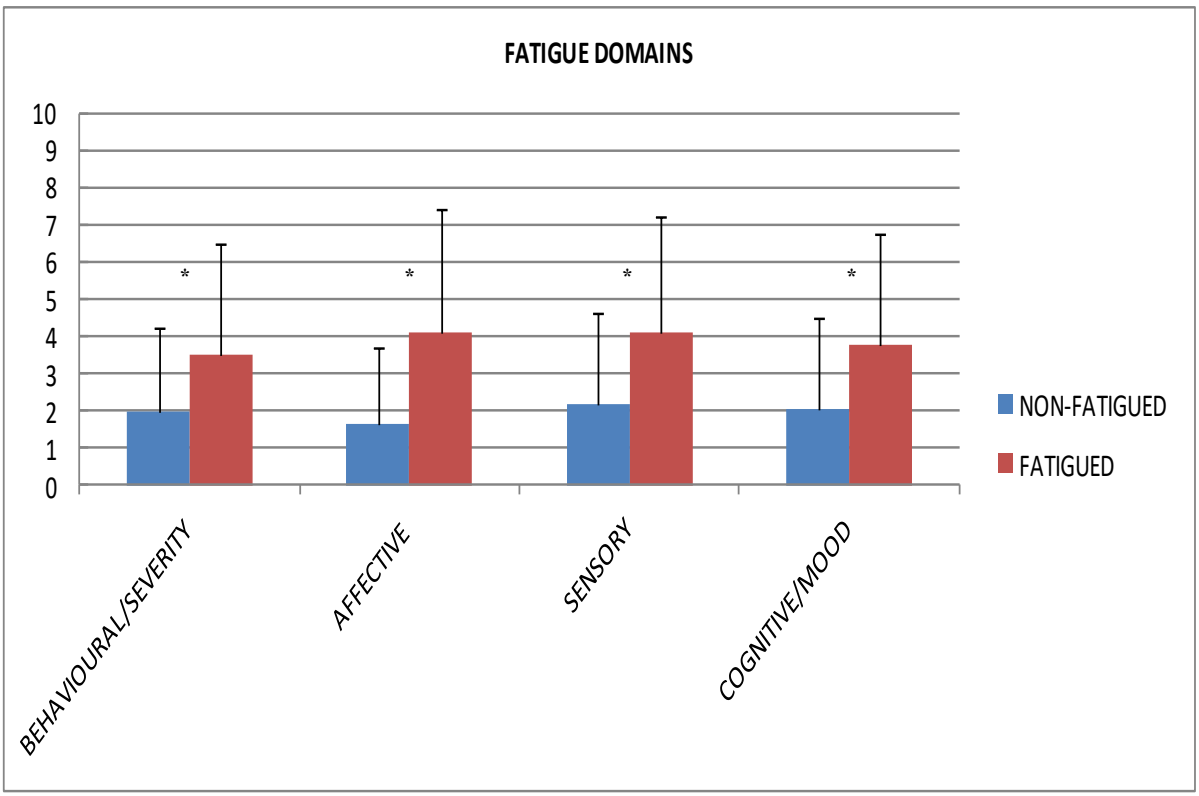
**Figure 2.** Graphic visualization of intra-group differences for time courses of fatigue.




**P<.05***

Calculations based on analyses of variance (ANOVA) and 95% confidence intervals.

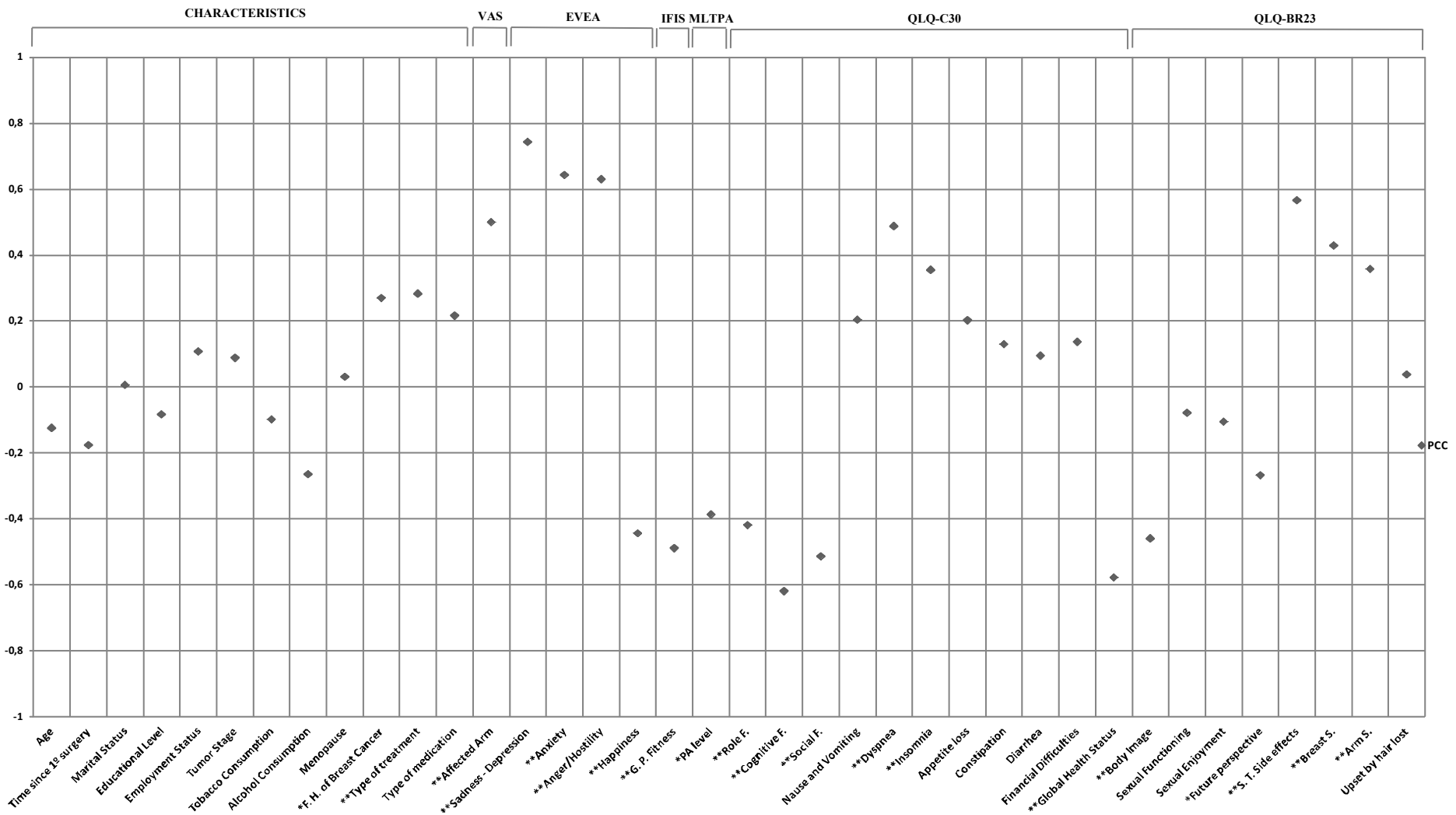
**Figure 3.** Graphic visualization of between-group differences for the Piper Fatigue Scale domains scores at the reassessment.




**P<.05***

Analysis of variance (ANOVA) and 95% Confidence Intervals.

**Figure 4.** Pearson's correlation coefficient for persistent cancer-related fatigue using the Piper Fatigue Scale Total Score at reassesment.



**P<.05* / P<.001****

**Abbreviations:** F. H. = Family History, VAS = Visual Analogue Scale, EVEA = Scale for Mood Assessment, IFIS = International Fitness Scale, G. P. Fitness = General Physical Fitness, MLTPA: Minnesota Leisure Time Physical Activity, PA level= Physical Activity level, F. = Functioning, S. T. = Systemic therapy, S. = Symptoms, QLQ = Quality of Life Questionnaire, PCC = Pearson's correlation coefficient.