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Determinants of long-term fatigue in breast cancer survivors: results of a prospective patient cohort study

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Abstract

***Objective*: Fatigue is among the most distressing symptoms across the breast cancer continuum. However, little is known about the factors contributing to long-term persisting fatigue. Therefore, we explored determinants of long-term physical, affective, and cognitive fatigue in a prospective cohort of breast cancer patients.**

***Methods*: Breast cancer patients recruited in a population-based case–control study (MARIE study) provided comprehensive data on sociodemographics, lifestyle, and preexisting medical conditions. At follow-up (median 6.3 years post-diagnosis, MARIEplus), disease-free cancer survivors ($N = 1928$) reported current fatigue using a validated multidimensional questionnaire. Additionally, survivors retrospectively rated their fatigue levels before diagnosis, during the treatment phase, and 1 year post-surgery. Linear regression analyses were performed.**

***Results*: As major determinants of long-term physical, affective, and cognitive fatigue, multiple regression analyses revealed preexisting psychological or depressive disorders, migraine, analgesic use, peripheral arterial obstructive disease (PAOD), and arthritis. A physically inactive lifestyle and obesity were associated with persisting physical fatigue. Aromatase inhibitors were also associated with long-term fatigue, especially cognitive fatigue. Chemotherapy and, to a lower extent, radiotherapy were major contributors to the development of fatigue during the treatment phase, yet were not associated with long-term fatigue.**

***Conclusions*: Although the development of fatigue in breast cancer patients seems largely impacted by cancer therapy, for the long-term persistence of fatigue, preexisting medical or psychological conditions related to depression or pain and lifestyle factors appear to be more relevant. Physicians, psycho-oncologists, and researchers may need to distinguish between acute fatigue during therapy and long-term persisting fatigue with regard to its pathophysiology and treatment.**

Background

Cancer-related fatigue (CRF) is among the most distressing symptoms across the breast cancer continuum with a severe impact on quality of life [1–4]. However, severity, duration, and course of fatigue vary widely between individuals. While some patients never experience CRF, the majority develops severe fatigue during cancer treatment, from which some recover after completion of treatment. In others, fatigue persists for months or even years [4,5]. CRF is subjective in nature, described by patients as exhaustion or loss of activity with respect to physical, emotional, or cognitive functions [6,7]. Hence, it is a multidimensional symptom. Although the underlying pathophysiology is still largely unclear, it is generally accepted that CRF is of multicausal origin. Cancer treatment appears to be one contributing factor [8,9]. A review of existing studies found that between 80% and 96% of breast cancer patients undergoing chemotherapy and between 60% and 93% receiving adjuvant radiotherapy have reported fatigue [9]. Psychological predispositions such as depressive disorders, somatization, catastrophizing, and anxiety have also frequently been associated with fatigue [5,8,10]. Furthermore, reduced physical activity and loss of muscle mass or strength may contribute to fatigue [11]. Different factors may be responsible for precipitating fatigue than for perpetuating fatigue. So far, most studies on fatigue in cancer survivors had been cross-sectional, investigating associated factors at a given time point. A recent longitudinal study investigated fatigue in 60 patients with various malignancies before, shortly after, and 1 year after cancer treatment, revealing cognitive behavioral factors but not cancer diagnosis nor treatment as predictive factors for fatigue 1 year post-treatment [12].

However, data on factors contributing to long-term persistence of fatigue are scarce, and the multidimensional nature of fatigue has so far rarely been considered.

Therefore, taking the different fatigue dimensions into account, we investigated determinants of long-term fatigue about 6 years after cancer diagnosis in a prospective breast cancer cohort and also explored precipitating factors of CRF.

Methods

Study setting

Incident breast cancer patients aged 50 to 75 years were recruited in a population-based case–control study conducted in 2002–2005 in two regions in Germany (MARIE study [13]). Patients (cases) were eligible if they had a histologically confirmed primary invasive or *in situ* breast cancer and being a resident of one of the study regions. All patients had undergone breast surgery. In 2009, a follow-up of the cases was performed (MARIEplus study [14]). Out of the 3813 MARIE cases, 507 were deceased, and one was lost to follow-up. Of the remaining 3305 cases, 2327 (70%) completed a fatigue questionnaire. We excluded 209 cases with a relapse, metastases, or second tumors, 32 cases with missing pre-diagnosis fatigue data, and 158 with high pre-diagnosis fatigue level ($\geq$7 on a 0–10 scale), because these women either suffered from fatigue already before cancer treatment or had misinterpreted the 0–10 scale. Thus, this analysis included 1928 disease-free survivors without substantial fatigue before breast cancer diagnosis.

The MARIE/MARIEplus study was approved by the ethics committee of the University of Heidelberg and the Medical Council of Hamburg. All subjects gave written informed consent prior to participation in the study.

Assessment of patient characteristics and clinical data

Baseline data were assessed in standardized personal interviews at a median of 17 weeks (interquartile range (Q1, Q3) = (2, 55)) after cancer diagnosis. Educational level was derived from the highest degree reached at school, vocational training, or at university. The physical activity level was calculated by summing the average hours per week spent walking, cycling, or engaging in sports weighted by metabolic equivalents according to the compendium of Ainsworth *et al.* [15]. Pre-existing diseases diagnosed by a physician before baseline as well as regularly used medications (for at least a year) were self-reported using checklists. A woman was classified as having psychic/depressive disorders if she had been diagnosed with a depression by a physician or had regularly used psychotropic drugs. Cancer characteristics and treatment data were abstracted from hospital and pathology records.

Fatigue assessment

Fatigue at time of follow-up (median 6.3 years post-diagnosis, (Q1, Q3) = (5.4, 7.1)) was assessed with the self-administered 20-item Fatigue Assessment Questionnaire, which had been found by factor analysis to cover the physical, affective, and cognitive dimensions of fatigue [7]. Scores were derived by summing the answers (0 = not at all, 1 = a little, 2 = quite a bit, 3 = very much) of the appropriate items. All scores were linearly rescaled to a 0–100 scale. Additionally, the questionnaire includes a rating scale ranging from 0 (not tired at all) to 10 (totally exhausted). This scale is equivalent to the average fatigue intensity rating of the Fatigue Symptom Inventory [16]. Using this rating scale, the cancer survivors rated besides their current fatigue at follow-up also retrospectively the levels of fatigue experienced 1 year after breast surgery, during radiotherapy and during chemotherapy (if applicable), shortly after breast surgery, and in the year before cancer diagnosis.

Statistical analyses

Linear regression evaluations were performed with the physical, affective, and cognitive fatigue scores at follow-up as dependent variables. As independent variables, we investigated potentially relevant factors assessed at baseline including age, education, occupational status, children, marital status, and living alone or with others, as well as pre-diagnosis body mass index (BMI), leisure-time physical activity, alcohol intake, and medical conditions existing already before cancer diagnosis, that is, preexisting psychological or depressive disorders, diagnosis of migraine, arthritis, PAOD, diabetes, osteoporosis, thyroid disorders, use of antihypertensive medication, use of menopausal hormone therapy, use of insulin, use of other hormones (e.g., thyroid hormones), tranquilizers, or analgesics. Further variables considered in the analyses were cancer-related factors, that is, tumor size, grading, number of affected nodes, estrogen and progesterone receptor status (ER/PR), and cancer treatment. Treatment was classified as chemotherapy alone (CT), radiotherapy alone (RT), sequential CT and RT, 'sandwich therapy' (CT–RT–CT), and surgery alone (without CT or RT). Use of tamoxifen and of aromatase inhibitors was also assessed. For smoking, we considered pre-diagnosis and post-diagnosis behavior. Models were adjusted for the rating of the pre-diagnosis fatigue level. Different transformations of the dependent variables were investigated, but the untransformed variables best matched a normal distribution of residuals. All variables were entered in the model simultaneously, and variables that neither showed a significant association with any dependent variable nor had a confounding effect on other covariates were then dropped from the final model. Colinearity diagnostics indicated no violations among the variables in our model (all variance inflation factors $<$7).

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Additionally, to explore precipitating factors of fatigue in contrast to factors contributing to persistent fatigue, multivariate general linear models for repeated measures were calculated with the fatigue levels during treatment, 1 year after surgery, and at follow-up as dependent variables, controlled for pre-diagnosis fatigue level, investigating the same covariates as above.

Reported *p*-values are two-sided with a significance level of 0.05. SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA) was used.

Results

The distribution of patient characteristics is included in Table 1. Participants had a median age of 63 years at diagnosis. The majority (59.0%) of patients had small breast tumors classified as T1, 28.8% had T2, and 6.6% *in situ* carcinomas; only 3.1% had T3 or T4 tumors. In 74.2% of patients, lymph nodes were not involved. Estrogen and progesterone receptor status was positive (ER+/PR+) in 60.7% and negative (ER−/PR−) in 14.1% of patients (data not shown).

Table 1. Multiple linear regression models on the different fatigue dimensions about 6 years post-diagnosis

		Fatigue at follow-up (FAQ scale 0–100)					
		Physical dimension ($R^2 = 25.0$)		Affective dimension ($R^2 = 22.0$)		Cognitive dimension ($R^2 = 15.3$)	
Covariates included in the model	***n***	***β***	**(95% CI)**	***β***	**(95% CI)**	***β***	**(95% CI)**
Pre-diagnosis fatigue level	1928	**4.67**	**(4.00, 5.35)******	**4.13**	**(3.47, 4.79)******	**3.96**	**(3.25, 4.68)******
Age at diagnosis		−0.01	(−0.21, 0.19)	**−0.64**	**(−0.83, −0.44)******	**−0.27**	**(−0.48, −0.06)***
Education							
Basic	1056	**7.47**	**(4.30, 10.63)******	**5.77**	**(2.67, 8.86)*****	**4.17**	**(0.80, 7.54)***
Advanced	560	3.38	(−0.01, 6.77)	2.31	(−1.01, 5.63)	1.18	(−2.47, 4.75)
High	312	0.00	Ref.	0.00	Ref.	0.00	Ref.
Having children (yes versus no)	1587	2.14	(−0.74, 5.02)	1.37	(−1.45, 4.20)	1.55	(−1.52, 4.61)
Living with others (yes versus no)	1416	−1.31	(−3.20, 0.58)	0.55	(−1.30, 2.40)	−0.80	(−2.82, 1.21)
BMI at diagnosis							
Obese	218	**6.89**	**(3.14, 10.63)*****	2.07	(−1.58, 5.71)	2.30	(−1.68, 6.28)
Overweight	573	**2.74**	**(0.19, 5.30)***	0.41	(−2.09, 2.91)	0.83	(−1.88, 3.55)
Underweight	180	4.30	(−0.98, 9.59)	−0.06	(−5.11, 5.24)	2.11	(−3.51, 7.73)
Normal	957	0.00	Ref.	0.00	Ref.	0.00	Ref.
Smoking							
Quit post diagnosis	100	0.85	(−4.06, 5.77)	2.65	(−2.14, 7.44)	−1.02	(−6.22, 4.17)
Reduced post diagnosis	66	3.00	(−2.96, 8.97)	1.06	(−4.78, 6.90)	−1.13	(−7.46, 5.20)
Smoking (unchanged behavior)	98	2.06	(−2.96, 7.07)	4.14	(−0.75, 9.03)	2.20	(−3.10, 7.50)
No smoking at or after diagnosis	1614	0.00	Ref.	0.00	Ref.	0.00	Ref.
Physical activity pre-diagnosis							
First quintile	379	**4.49**	**(0.87, 8.11)***	2.89	(−0.65, 6.43)	2.52	(−1.32, 6.36)
Second quintile	386	1.75	(−1.83, 5.32)	0.87	(−2.63, 4.36)	1.86	(−1.93, 5.65)
Third quintile	407	1.52	(−1.98, 5.01)	0.39	(−3.03, 3.82)	−0.18	(−3.89, 3.53)
Fourth quintile	407	−1.13	(−4.62, 2.37)	−0.66	(−4.09, 2.76)	1.77	(−1.94, 5.47)
Fifth quintile	333	0.00	Ref.	0.00	Ref.	0.00	Ref.
Therapy							
Only RT	889	0.00	Ref.	0.00	Ref.	0.00	Ref.
CT and RT	631	2.00	(−0.56, 4.56)	−0.76	(−3.26, 1.74)	1.02	(−1.70, 3.74)
CT–RT–CT	54	4.03	(−2.73, 10.79)	3.48	(−3.13, 10.10)	3.97	(−3.25, 11.19)
Only CT	131	3.44	(−1.03, 7.91)	1.51	(−2.86, 5.87)	2.10	(−2.61, 6.82)
Only surgery	232	−0.25	(−3.77, 3.27)	1.55	(−1.89, 5.00)	0.11	(−3.62, 3.84)
Aromatase (yes versus no)	1221	**2.55**	**(0.27, 4.83)***	**2.83**	**(0.60, 5.06)***	**3.60**	**(1.17, 6.02)****
Tamoxifen (yes versus no)	819	1.35	(−1.09, 3.78)	−0.79	(−3.17, 1.58)	−0.43	(−3.01, 2.16)
Pre-existing conditions (yes versus no):							
Psychic/depressive disorders	236	**10.30**	**(6.83, 13.77)******	**14.78**	**(11.39, 18.18)******	**10.45**	**(6.76, 14.14)******
Migraine	431	**4.38**	**(1.73, 7.03)****	**4.89**	**(2.29, 7.48)*****	**4.75**	**(1.94, 7.56)*****
Arthritis	953	**5.32**	**(3.05, 7.59)******	**3.15**	**(0.93, 5.37)****	**2.80**	**(0.39, 5.21)***
PAOD	181	**7.65**	**(3.89, 11.40)******	**4.28**	**(0.61, 7.95)***	**8.91**	**(4.93, 12.89)******
Diabetes	128	3.22	(−1.21, 7.65)	−2.70	(−7.04, 1.63)	1.53	(−3.17, 6.23)
Anti-hypertensive medication	722	2.23	(−0.14, 4.59)	−0.16	(−2.47, 2.15)	−0.56	(−3.07, 1.95)
Other hormone use[a]	500	**2.61**	**(0.12, 5.09)***	0.87	(−1.57, 3.32)	1.70	(−0.95, 4.34)
Analgesic use	232	**8.47**	**(4.98, 11.97)******	**4.34**	**(0.92, 7.77)***	**5.01**	**(1.29, 8.74)****
Tranquilizer use	201	2.32	(−1.37, 6.01)	**6.66**	**(3.03, 10.28)*****	2.48	(−1.45, 6.41)

FAQ, Fatigue Assessment Questionnaire; CI, confidence interval; CT, chemotherapy; RT, radiotherapy; PAOD, peripheral artery obstructive disease.
Bold emphasis highlight the statistically relevant results.
[a]Includes hormones other than menopausal hormones or insulin, for example, thyroid hormones, prednisolon.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$.

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At follow-up, the median (Q1, Q3) physical fatigue score was 30.3 (13.4, 57.6). Affective fatigue had a median (Q1, Q3) of 26.7 (6.7, 46.7) and cognitive fatigue of 22.2 (11.1, 44.4). The correlations between the different fatigue dimensions were as follows: r(physical, affective) = 0.69, r(physical, cognitive) = 0.68, r(affective, cognitive) = 0.66. The supplemental fatigue rating on the 0–10 scale for long-term fatigue at follow-up correlated well with the multi-item physical fatigue score (r = 0.86). Among those in the highest quartile of long-term physical fatigue score, the majority (92%) had increased fatigue levels also during treatment and 1 year post-surgery according to the fatigue ratings for the different time points. The median (Q1, Q3) rating of long-term fatigue on this 0–10 scale was 3 (2, 5). The median pre-diagnosis fatigue rating was 1 (0, 2); it increased to 3 (2, 6) after breast surgery, was highest during the treatment phase with 7 (3, 9), and decreased to 4 (2, 6) 1 year post-surgery.

Table 1 shows the results from the three multiple regression analyses on the different dimensions of long-term fatigue assessed with the multi-item Fatigue Assessment Questionnaire at follow-up. Lower education and preexisting psychological/depressive disorders, migraine, arthritis, PAOD, or analgesic use were major determinants of physical, affective, and cognitive fatigue. Low physical activity and obesity or overweight before diagnosis were additional independent determinants of physical fatigue. Use of aromatase inhibitors was also associated with long-term fatigue, especially with the cognitive fatigue dimension. The models explained 25.0%, 20.0%, and 15.3% of the variance of physical, affective, and cognitive fatigue, respectively.

Table 2 summarizes the results from the multivariate general linear model regressions on the fatigue levels during the treatment period, 1 year post-surgery, and at follow-up about 6 years post-diagnosis. Chemotherapy (alone or in combination with radiotherapy) was the strongest determinant of fatigue during treatment, followed by radiotherapy alone. However, therapy had a much weaker association with fatigue 1 year after surgery and no association with long-term persistent fatigue. Tumor characteristics (tumor size and ER/PR) showed significant associations with fatigue during treatment in models without the therapy variable (data not shown). However, when adding therapy to the model, only therapy but not the tumor characteristics remained significant, suggesting that the tumor characteristics are only indirectly associated with fatigue level, mediated by type of therapy.

The preexisting medical or psychological conditions associated with long-term fatigue were also significant determinants of fatigue during and post treatment. Body composition, physical inactivity, and low education were associated with long-term fatigue level, but not with development of fatigue during treatment. Smoking was associated with reduced fatigue during and post treatment.

Discussion

We found that preexisting medical or psychological conditions were major determinants of long-term physical, affective, and cognitive fatigue in disease-free breast cancer survivors about 6 years post-diagnosis. A physically inactive lifestyle and obesity were associated with persistent physical fatigue but not with affective or cognitive fatigue. Cancer therapy, especially chemotherapy, appeared as major precipitating factor for fatigue in breast cancer patients. However, it was not associated with long-term persisting fatigue.

Several previous studies showed that patients receiving chemotherapy or radiotherapy may suffer from fatigue [2,8,17–27]. It is an interesting finding of our study that chemotherapy and radiotherapy, although major contributors to the development of fatigue, have no influence on long-term persistence of fatigue in survivors. Our finding is in line with another prospective follow-up study, which observed that cancer treatment did not predict persistent fatigue 1 year post-treatment [12]. Other mechanisms appear responsible for the persistence of fatigue after the end of treatment. Our data suggest that two different types of fatigue might be distinguished: (1) fatigue that is mainly related to chemotherapy and radiotherapy and resolves after end of therapy; and (2) fatigue emerging during therapy and persisting months or years after end of therapy, which appears to be associated with preexisting depressive or psychological disorders and factors related to pain, such as the use of analgesics, migraine, and arthritis and PAOD. Possible common underlying mechanisms of these disorders are dysregulations in stress hormones or cytokines, hypothalamic dysfunction, or mitochondrial dysfunction [28]. It can be speculated that in patients with such preexisting dysregulations, damages induced by chemotherapy or radiotherapy such as severe oxidative stress, inflammation, or circadian rhythm disruption may not be manageable by the body, thus resulting in the persistence of fatigue. Symptom clusters between fatigue, depression, and pain have been observed previously, and it has been proposed by some authors that fatigue associated with pain and depression has a different pathophysiology than fatigue unrelated to these disorders [24,28–33]. Our findings may support this hypothesis.

Further, a physically inactive lifestyle before cancer diagnosis was associated with persistence of fatigue in our study. Patients physically inactive before diagnosis tend to be also inactive during and after cancer treatment [34]. Thus, our data may indicate that a physically inactive lifestyle contributes to persistence of fatigue, strengthening the recommendation of the American College of Sports Medicine for cancer survivors, which stated that 'avoiding inactivity is likely helpful' [35]. In line with other studies [36–38], we identified obesity as a determinant of persisting (physical) fatigue. Underweight

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Table 2. Multivariate linear regression analysis on fatigue at different time points

	Fatigue level (scale 0–10)					
	During treatment ($R^2 = 25.9$)		One year post-surgery ($R^2 = 22.1$)		At follow-up ($R^2 = 23.0$)	
Covariates included in the model	β	**(95% CI)**	β	**(95% CI)**	β	**(95% CI)**
Pre-diagnosis fatigue level	**0.42**	**(0.34, 0.50)******	**0.49**	**(0.42, 0.56)******	**0.48**	**(0.42, 0.54)******
Age at diagnosis	**−0.07**	**(−0.09, −0.05)******	**−0.08**	**(−0.10, −0.06)******	−0.01	(−0.03, 0.01)
Education						
Basic	0.36	(−0.01, 0.73)	**0.37**	**(0.03, 0.71)***	**0.41**	**(0.12, 0.70)****
Advanced	0.03	(−0.37, 0.42)	0.04	(−0.32, 0.41)	0.23	(−0.08, 0.54)
High	0.00	Ref.	0.00	Ref.	0.00	Ref.
Having children (yes versus no)	0.25	(−0.08, 0.59)	**0.36**	**(0.05, 0.67)***	0.17	(−0.10, 0.43)
Living with others (yes versus no)	−0.17	(−0.40, 0.06)	−0.19	(−0.41, 0.02)	−0.12	(−0.30, 0.06)
BMI at diagnosis						
Obese	0.09	(−0.35, 0.52)	0.24	(−0.16, 0.65)	0.33	(−0.01, 0.67)
Overweight	0.00	(−0.30, 0.30)	−0.05	(−0.23, 0.32)	0.07	(−0.16, 0.30)
Underweight	0.40	(−0.22, 1.02)	0.22	(−0.36, 0.79)	**0.53**	**(0.06, 1.03)***
Normal	0.00	Ref.	0.00	Ref.	0.00	Ref.
Smoking						
Quit post diagnosis	−0.54	(−1.12, 0.03)	−0.08	(−0.61, 0.45)	0.06	(−0.39, 0.51)
Reduced post diagnosis	−0.48	(−1.17, 0.21)	−0.26	(−0.89, 0.37)	0.13	(−0.41, 0.66)
Smoking (unchanged behavior)	**−0.81**	**(−1.40, −0.22)****	**−0.69**	**(−1.23, −0.15)***	0.13	(−0.33, 0.59)
No smoking at or after diagnosis	0.00	Ref.	0.00	Ref.	0.00	Ref.
Physical activity pre-diagnosis						
First quintile	−0.06	(−0.49, 0.37)	−0.08	(−0.47, 0.32)	**0.49**	**(0.15, 0.82)****
Second quintile	0.21	(−0.20, 0.63)	0.13	(−0.25, 0.51)	0.26	(−0.06, 0.59)
Third quintile	0.19	(−0.22, 0.59)	0.08	(−0.29, 0.46)	0.21	(−0.11, 0.53)
Fourth quintile	0.23	(−0.18, 0.64)	0.20	(−0.17, 0.58)	0.05	(−0.27, 0.37)
Fifth quintile	0.00	Ref.	0.00	Ref.	0.00	Ref.
Therapy						
Only RT	0.00	Ref.	0.00	Ref.	0.00	Ref.
CT and RT	**1.92**	**(1.62, 2.22)******	**0.66**	**(0.39, 0.93)******	0.13	(−0.10, 0.36)
CT–RT–CT	**1.80**	**(1.00, 2.60)******	**1.22**	**(0.49, 1.96)****	0.21	(−0.41, 0.84)
Only CT	**1.75**	**(1.23, 2.27)******	**0.82**	**(0.34, 1.30)*****	0.38	(−0.03, 0.78)
Only surgery	**−1.27**	**(−1.70, −0.84)******	**−0.55**	**(−0.95, −0.16)****	0.04	(−0.29, 0.38)
Aromatase (yes versus no)	0.11	(−0.16, 0.38)	0.19	(−0.06, 0.43)	0.13	(−0.08, 0.34)
Tamoxifen (yes versus no)	−0.07	(−0.36, 0.21)	0.16	(−0.10, 0.42)	**0.24**	**(0.01, 0.46)***
Pre-existing conditions (yes versus no):						
Psychic/depressive disorders	**0.67**	**(0.27, 1.07)****	**0.78**	**(0.41, 1.16)******	**0.76**	**(0.45, 1.08)******
Migraine	**0.47**	**(0.16, 0.78)*****	**0.48**	**(0.20, 0.76)*****	**0.46**	**(0.22, 0.70)*****
Arthritis	**0.42**	**(0.16, 0.69)****	**0.43**	**(0.18, 0.67)*****	**0.40**	**(0.19, 0.60)*****
PAOD	**0.48**	**(0.04, 0.92)***	**0.75**	**(0.34, 1.15)*****	**0.49**	**(0.15, 0.83)****
Diabetes	−0.13	(−0.65, 0.39)	−0.17	(−0.65, 0.31)	−0.05	(−0.45, 0.36)
Antihypertensive medication	0.24	(−0.04, 0.51)	**0.46**	**(0.21, 0.72)*****	**0.25**	**(0.04, 0.47)***
Other hormone use[a]	**0.46**	**(0.17, 0.75)****	**0.42**	**(0.15, 0.69)****	0.19	(−0.04, 0.42)
Analgesic use	**0.52**	**(0.11, 0.92)***	**0.43**	**(0.06, 0.81)***	**0.55**	**(0.23, 0.86)*****
Tranquilizer use	0.36	(−0.07, 0.79)	0.08	(−0.31, 0.48)	0.14	(−0.19, 0.48)

CI, Confidence interval; CT, Chemotherapy; RT, Radiotherapy; PAOD, peripheral artery obstructive disease.
[a]Includes hormones other than menopausal hormones or insulin, for example, thyroid hormones, prednisolon.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$.

was also associated with increased long-term fatigue ratings. Although we cannot draw causal inference from our analysis, patients with an unhealthy body composition or a physically inactive lifestyle appear to be at higher risk for prolonged fatigue. Further investigation of these associations within prospective trials is warranted.

Data on the effect of smoking on CRF are scarce. We observed that patients who continued smoking after the cancer diagnosis reported lower levels of fatigue during therapy. It is known from several studies that nicotine can improve attention, memory, and performance [39]. Nevertheless, we observed no benefits in terms of long-term fatigue. The general adverse health effects of smoking outweigh potential short-term benefits by far.

Use of aromatase inhibitors was a significant, moderate determinant of the cognitive dimension of long-term fatigue. Cognitive dysfunction has been identified as a possible consequence of aromatase inhibitor therapy, but previous results were inconclusive [40].

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The regression models explained between 15.3% and 25.0% of the variance of the different long-term fatigue dimensions. Although we investigated a wide spectrum of potential influencing factors and given the fact that a large proportion of the variance may be based on the subjectivity of the individual fatigue experience, there might be other relevant factors not considered within our study.

To our knowledge, with 1928 disease-free breast cancer survivors, this is the largest study investigating determinants of CRF. A strength of this study is the detailed, multidimensional assessment of long-term fatigue about 6 years post-diagnosis that enabled investigation of different fatigue dimensions. Although previous studies mostly used a dichotomous fatigue variable, we also considered intensity of fatigue and accounted for pre-diagnosis fatigue levels in the regression models.

We performed supplementary analyses regarding fatigue during treatment and 1 year post-surgery. These fatigue ratings were based on single 0–10 rating scales and as such clearly highly subjective. It should be noted that those analyses were explorative analyses, providing some insights on precipitating factors in contrast to factors contributing to persistent fatigue, which should be further investigated and verified in future studies. Although all results on long-term persistence are based on current fatigue, the fatigue levels at earlier time points were assessed retrospectively, which might be prone to recall error with unclear direction. Yet, this retrospective rating also provides some benefits over longitudinal fatigue assessment. For example, before treatment, the meaning of a subjective fatigue rating of, for example, '5' on a 0–10 Likert scale may not be equivalent to a rating of '5' after completion of adjuvant therapy, because the experience of unusually severe fatigue during chemotherapy or radiotherapy may have shifted the perception of severity. This phenomenon is called 'response shift' and can cause misleading results. Significant response shifts in ratings of average fatigue have been observed in longitudinal studies with breast cancer patients [19,41,42]. In contrast, women may recall well whether fatigue worsened or improved from one period to another. Hence, as we analyzed the fatigue ratings during and after therapy relative to the pre-diagnosis fatigue level, results may well reflect fatigue increases or decreases over the course of time.

A limitation of our study is that at the time of follow-up, 507 patients were already deceased, and of the remaining survivors, 30% did not respond to the fatigue questionnaire. Hence, the most severely diseased or fatigued patients might have been lost for our analyses. Although determinants of fatigue may differ between severely diseased late-stage cancer patients and other cancer patients, it seems unlikely that determinants of development or persistence of fatigue in disease-free breast cancer survivors are substantially affected by the moderate participation rate or by the exclusion of deceased participants. Further, although preexisting diseases and medications were assessed in face-to-face interviews along standardized checklists, those conditions were self-reported and thus prone to error.

In conclusion, this large study indicates that determinants of long-term physical fatigue include low physical activity, obesity, and lower education. Beyond these lifestyle factors, major determinants of long-term fatigue were factors related to depression and pain, including preexisting psychological or depressive disorders, migraine, analgesic use, PAOD, and arthritis. Those disorders appear to predispose cancer patients to develop persistent fatigue. Use of aromatase inhibitors was significantly associated with fatigue, especially on the cognitive fatigue dimension. Chemotherapy or radiotherapy, however, despite being major determinants of developing fatigue during the treatment phase, were not associated with long-term persisting fatigue in breast cancer survivors. Physicians, psycho-oncologists, and researchers may need to distinguish between acute fatigue during therapy and long-term persisting fatigue with regard to its pathophysiology and treatment.

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Conflict of interest

The authors have declared no conflict of interest.

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