Long-Term Longitudinal Patterns of Patient-Reported Fatigue After Breast Cancer: A Group-Based Trajectory Analysis

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PURPOSE Fatigue is recognized as one of the most burdensome and long-lasting adverse effects of cancer and cancer treatment. We aimed to characterize long-term fatigue trajectories among breast cancer survivors.

METHODS We performed a detailed longitudinal analysis of fatigue using a large ongoing national prospective clinical study (CANcer TOxicity, ClinicalTrials.gov identifier: NCT01993498) of patients with stage I-III breast cancer treated from 2012 to 2015. Fatigue was assessed at diagnosis and year 1, 2, and 4 postdiagnosis. Baseline clinical, sociodemographic, behavioral, tumor-related, and treatment-related characteristics were available. Trajectories of fatigue and risk factors of trajectory-group membership were identified by iterative estimates of group-based trajectory models.

RESULTS Three trajectory groups were identified for severe global fatigue (n = 4,173). Twenty-one percent of patients were in the high-risk group, having risk estimates of severe global fatigue of 94.8% (95% CI, 86.6 to 100.0) at diagnosis and 64.6% (95% CI, 59.2 to 70.1) at year 4; 19% of patients clustered in the deteriorating group with risk estimates of severe global fatigue of 13.8% (95% CI, 6.7 to 20.9) at diagnosis and 64.5% (95% CI, 57.3 to 71.8) at year 4; 60% were in the low-risk group with risk estimates of 3.6% (95% CI, 2.5 to 4.7) at diagnosis and 9.6% (95% CI, 7.5 to 11.7) at year 4. The distinct dimensions of fatigue clustered in different trajectory groups than those identified by severe global fatigue, being differentially affected by sociodemographic, clinical, and treatment-related factors.

CONCLUSION Our findings highlight the multidimensional nature of cancer-related fatigue and the complexity of its risk factors. This study helps to identify patients with increased risk of severe fatigue and to inform personalized interventions to ameliorate this problem.
METHODS

Data Source
CANTO cohort data were used. Briefly, CANTO enrolled female patients with stage I-II-III BC. Data used in the present study had been collected at diagnosis (baseline, before treatment onset) and then at year 1 (3–6 months after completion of primary surgery, chemotherapy, and/or radiation therapy), 2, and 4 follow-up visits after diagnosis. Adjuvant endocrine and/or antihuman epidermal growth factor receptor 2 (HER2) treatment was allowed during follow-up. All participants signed informed consent.

Study Cohort
Six thousand six hundred nineteen women diagnosed with BC from 2012 to 2015, with a follow-up of at least 4 years after diagnosis were initially included. Patients who did not respond to the baseline (diagnosis, before the treatment onset) fatigue assessment and did not have follow-up visit were excluded. The potential for bias in selection was evaluated by comparing respondents and nonrespondents. The latter were older, with more comorbidities, lower income, and higher-stage BC. However, no significant differences were present (data are not shown). The final analytic cohort included 5,692 patients (the flowchart of inclusion is available in the Data Supplement, online only).

Variables of Interest

Outcome variable. The primary outcome of interest was global fatigue, assessed by the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [QLQ]-C30. Secondly, we evaluated the physical, emotional, and cognitive dimensions of fatigue using the EORTC QLQ-FA12. Both instruments provide a four-point Likert scale response for each item: not at all, a little, quite a bit, and very much. All items are converted to a 0–100 scale using a standard scoring algorithm, where higher scores reflect greater fatigue severity. All outcomes were defined as a binary variable, with scores $\geq 40$ of 100 defining severe fatigue (threshold defined per Abrahams et al for global fatigue and retained for the distinct dimensions on the basis of correlation analyses showing good concordance [data not shown]).

Exposure variables. Data collected by medical record review at diagnosis included age; socioeconomic status including education level and income; marital status; Charlson comorbidity index; tobacco use; body mass index (BMI); physical activity; tumor stage; breast surgery; axillary management; and receipt of radiotherapy, chemotherapy, endocrine therapy, and antihuman HER2 therapy. Patient-reported outcomes were collected at diagnosis including pain and insomnia assessed as per EORTC-QLQC30, physical activity as per Global Physical Activity Questionnaire-16, and depression and anxiety as per the Hospital Anxiety and Depression Scale. In addition, hot flashes at diagnosis were assessed by in-person nurse evaluations (Common terminology criteria for adverse events v4.0).

Statistical Analysis
Patient characteristics were descriptively summarized for the whole cohort.

Definition of Trajectory Groups
Multivariable latent class models using Group-Based Trajectory Modeling (GBTM) assessed longitudinal variations in repeated measures of fatigue. The procedure is extensively presented in the Data Supplement. Each
identified trajectory group was assigned a label name that briefly describes the associated fatigue outcome pattern. Characteristics in each group were then descriptively summarized.

**Predictors of Trajectory-Group Membership**

Risk factors for group membership with trajectory groups were identified after the definition of the best-fitting model, exponentiating model-based estimates to obtain odds ratios and respective 95% CIs. Membership to the trajectory group with the lowest risk levels of severe fatigue over time was chosen as a reference to assess risk factors for clustering into groups with worse fatigue patterns.

**Sensitivity Analyses**

We used an extension of GBTM to address potential nonrandom participant dropout (eg, truncation because of BC recurrence, second cancer, or death events) that may vary across groups. In addition, subgroup analyses by systemic treatment received were performed to assess membership risk factors.

Statistical analysis was performed using SAS statistical software version 9.4 (SAS Institute Inc) and the PROC TRAJ Procedure developed for SAS. Statistical significance was defined with a two-sided P value < .05.

**RESULTS**

**Cohort Characteristics**

Among the whole cohort (N = 5,692), the mean age at diagnosis was 56.2 years (standard deviation = 11.3); 56.3% had a household income < 3,000 Euros/month. The majority of the cohort did not have relevant comorbidities (79.8%). Altogether, 50% of patients had stage I BC. Sixty-one percent of patients had anxiety symptoms, and 18.2% depressive symptoms at diagnosis. Of note, the proportion of borderline or case anxiety was highest at diagnosis (61% of patients), reduced at year 1 (44.6%), and plateaued over time at year 2 (44.4%) and year 4 (43.5%) after diagnosis. Overall, 73.2% had breast-conserving surgery, 90.9% received radiotherapy, 53.2% received chemotherapy, 81.4% received hormonal therapy, and 11.8% received anti-HER2 therapy. The prevalence of severe fatigue over 4 years reached 35.6% for global fatigue, 35.0% for physical, 25.4% for emotional, and 13.3% for cognitive fatigue. Cohort characterization and fatigue metrics over time are provided in the Data Supplement.

**Definition of Trajectory Groups**

Metrics used for model selection are available in the Data Supplement. On the basis of an average posterior probability of group membership close to or > .75, there was a relatively high degree of certainty in group assignment. The Maximum Likelihood Estimates parameters of the models are provided in the Data Supplement.

**Severe Global Fatigue**

Our final model (n = 4,173) identified three trajectory groups of severe global fatigue, graphically represented in Figure 1A. The first group (21% of patients; high) had a persistently high risk of severe global fatigue over time (estimated risk of severe fatigue 94.8% [95% CI, 86.6 to 100.0] at diagnosis and 64.6% [95% CI, 59.2 to 70.1] at year 4) with corresponding mean fatigue scores of 62.3 of 100 (95% CI for the mean, 61.2 to 63.5) at diagnosis and 52.1 of 100 (49.7 to 54.5) at year 4. In the second trajectory group (19%; deteriorating), the risk of severe fatigue was low at diagnosis and increased substantially over time (estimated risk of severe fatigue 13.8% [95% CI, 6.7 to 20.9] at diagnosis and 64.5% [95% CI, 57.3 to 71.8] at year 4), where fatigue started off with an excellent mean score at diagnosis (24.5 of 100, 95% CI for the mean, 23.7 to 25.4), but then increased significantly at year 1 not recovering by year 4 (51.3 of 100; 95% CI for the mean, 51.3 to 53.2). The best-performing trajectory group in terms of fatigue symptoms included the majority of patients in this analysis (60%; low), reporting a persistently low risk of severe global fatigue (estimated risk of severe fatigue 3.6% [95% CI, 2.5 to 4.7] at diagnosis and 9.6% [95% CI, 7.5 to 11.7] at year 4), with the highest mean score of 23.1 of 100 (95% CI for the mean, 22.3 to 23.8).

The Data Supplement displays the mean scores of fatigue over time of the identified groups and the observed and predicted risk of severe fatigue. The distribution of patient characteristics at diagnosis by trajectory group is presented in Table 1. Significant risk multivariable factors for membership to worse trajectory groups (high and deteriorating group) included age (younger age) and contextual (being single), behavioral (tobacco use), and clinical characteristics (comorbidities, high BMI, and symptoms at diagnosis). Particularly, among treatment-related factors, receipt of hormonal therapy was significantly associated with increased likelihood of membership to the deteriorating group compared with the low group, with an adjusted odds ratio (95% CI) of 1.38 (1.02 to 1.86).

**Domains of Fatigue**

The distinct dimensions of fatigue were clustered in different trajectory groups than those identified by severe global fatigue. For physical fatigue, the final model identified four trajectory groups of severe physical fatigue, graphically represented in Figure 1B. One group had high-risk estimates of severe physical fatigue over time (13% of patients; high). The risk of severe physical fatigue in the second trajectory group (23%; deteriorating) was low at diagnosis but increased over time. The third group represented patients with high-risk estimates of severe physical fatigue at diagnosis. By year 4, the risk estimate decreased being low (11%; recovery). Finally, the best trajectory group included most patients in this analysis.
(53%; low), reporting a persistently low risk estimate of severe physical fatigue over time. The distribution of patient characteristics at diagnosis by trajectory group is presented in Table 2. Significant multivariable risk factors for membership were similar to the ones reported for severe global fatigue. Consistent with models of global fatigue, hormonal therapy was associated with higher odds of belonging to the deteriorating group compared with low.

Similarly, the final model for severe emotional fatigue included four trajectory groups (Fig 1C). Ten percent of patients reported a high-risk estimate of severe emotional fatigue over time (high group), 15% of patients belonged to the recovery group, and the best trajectory group included the majority of patients in this analysis (56%; low) having a low-risk estimate of severe emotional fatigue over time. The distribution of patient characteristics at diagnosis by trajectory group is presented in Table 3. The most consistent associations were seen between emotional distress–related variables and emotional fatigue.

Finally, the model for severe cognitive fatigue included two trajectory groups (Fig 1D). The majority (79%) of patients clustered in the low trajectory group, and only 21% reported an overall high risk of severe cognitive fatigue (high group) over time. The distribution of patient characteristics at diagnosis by trajectory group and results for group membership are presented in Table 4, with age, smoking, having a mastectomy, and physical and emotional symptomatology at diagnosis increasing the risk of belonging to the high group.

Results of sensitivity analyses also showed great consistency regarding the number of trajectory groups identified and risk factors for long-term high or deteriorating fatigue trajectories. Particularly, the analyses yielded similar results regardless of subgrouping by systemic adjuvant treatment received (Data Supplement).

FIG 1. Trajectory groups according to the best-fitting prediction model of (A) severe global fatigue, (B) severe physical fatigue, (C) severe emotional fatigue, and (D) severe cognitive fatigue. Solid lines represent the predicted trajectories of risk estimate, and dashed lines represent the respective 95% CIs of risk estimate. T, time.
TABLE 1. Distribution of Patient Characteristics at Diagnosis and Breast Cancer Primary Treatment by Severe Global Trajectory Group and Multinomial Logistic Regression of Factors Associated With Severe Global Fatigue Trajectory-Group Membership (v group C: low, n = 2,489 [60%])

| Patient Characteristic                  | Group A: High (n = 890 [21%]) | Group B: Deteriorating (n = 794 [19%]) | Group C: Low (n = 2,489 [60%]) |
|----------------------------------------|-------------------------------|----------------------------------------|--------------------------------|
| Age, continuous (1-year increase), mean ± SD | 51.4 ± 11.0 0.93 (0.92 to 0.95) < .001 | 53.6 ± 10.8 0.97 (0.96 to 0.98) < .001 | 57.3 ± 11.0 |
| BMI, continuous, mean ± SD             | 25.9 ± 5.9 1.03 (1.00 to 1.06) .0220 | 26.6 ± 5.8 1.05 (1.03 to 1.07) < .001 | 25.4 ± 4.9 |
| Physical activity, GPAQ16, continuous, median (Q1-Q3) | 12.0 (0.0-40.0) 1.00 (1.00 to 1.00) .5097 | 13.7 (0.0-36.0) 1.00 (1.00 to 1.00) .954 | 16.0 (3.0-40.0) |
| Smoking behavior                       | < .001 | .005 |
| Current or former smoker               | 440 (49.4) 1.65 (1.26 to 2.15) | 362 (45.6) 1.38 (1.10 to 1.74) | 832 (33.4) |
| Never smoker                           | 450 (50.6) Ref | 432 (54.4) Ref | 1,657 (66.6) |
| Charlson                               | .003 | .187 |
| ≥ 1                                    | 205 (23.0) 1.65 (1.19 to 2.29) | 164 (20.7) 1.21 (0.91 to 1.60) | 445 (17.9) |
| 0                                      | 685 (77.0) Ref | 630 (79.3) Ref | 2,044 (82.1) |
| Marital status                         | .006 | .0248 |
| Not partnered                          | 270 (30.3) 1.58 (1.14 to 2.18) | 243 (30.6) 1.37 (1.04 to 1.80) | 625 (25.1) |
| Partnered                              | 620 (69.7) Ref | 551 (69.4) Ref | 1,864 (74.9) |
| Degree level                           | .5416 | .5479 |
| High school or higher                  | 794 (89.2) 1.16 (0.72 to 1.85) | 690 (86.9) 1.12 (0.78 to 1.61) | 2,133 (85.7) |
| Primary school                         | 96 (10.8) Ref | 104 (13.1) Ref | 356 (14.3) |
| Income, Euro/month                     | .5849 | .1546 |
| ≥ 3,000                                | 355 (39.9) 1.09 (0.81 to 1.46) | 310 (39.0) 1.20 (0.93 to 1.55) | 1,212 (48.7) |
| < 3,000                                | 535 (60.1) Ref | 484 (61.0) Ref | 1,277 (51.3) |
| BC stage                               | .3216 | .1604 |
| II/III                                 | 488 (54.8) 1.18 (0.85 to 1.66) | 456 (57.4) 1.22 (0.92 to 1.62) | 1,153 (46.3) |
| I                                      | 402 (45.2) Ref | 338 (42.6) Ref | 1,336 (53.7) |
| Mastectomy                             | 266 (29.9) 1.06 (0.74 to 1.52) | 230 (29.0) 1.09 (0.80 to 1.48) | 617 (24.8) |
| Partial breast surgery                  | 624 (70.1) Ref | 564 (71.0) Ref | 1,872 (75.2) |
| Radiation therapy                      | .8860 | .6997 |
| Yes                                    | 813 (91.3) 1.04 (0.62 to 1.73) | 735 (92.6) 1.09 (0.70 to 1.70) | 2,261 (90.8) |
| No                                     | 77 (8.7) Ref | 59 (7.4) Ref | 228 (9.2) |
| Chemotherapy                           | .1906 | .1610 |
| Yes                                    | 531 (69.7) 0.80 (0.57 to 1.12) | 502 (63.2) 1.23 (0.92 to 1.64) | 1,235 (49.6) |
| No                                     | 359 (40.3) Ref | 292 (36.8) Ref | 1,254 (50.4) |
| Hormonal therapy                       | .1101 | .0359 |
| Yes                                    | 718 (80.7) 1.32 (0.94 to 1.86) | 660 (83.1) 1.38 (1.02 to 1.86) | 2,010 (80.8) |
| No                                     | 172 (19.3) Ref | 134 (16.9) Ref | 479 (19.2) |
| Anti-HER2 therapy                      | .7765 | .8400 |
| Yes                                    | 119 (13.4) 1.06 (0.71 to 1.59) | 112 (14.1) 1.04 (0.74 to 1.46) | 281 (11.3) |
| No                                     | 771 (86.6) Ref | 682 (85.9) Ref | 2,208 (88.7) |

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TABLE 1. Distribution of Patient Characteristics at Diagnosis and Breast Cancer Primary Treatment by Severe Global Trajectory Group and Multinomial Logistic Regression of Factors Associated With Severe Global Fatigue Trajectory-Group Membership (v group C: low, n = 2,489 [60%]) (continued)

| Patient Characteristic | Group A: High (n = 890 [21%]) | Group B: Deteriorating (n = 794 [19%]) | Group C: Low (n = 2,489 [60%]) |
|------------------------|--------------------------------|--------------------------------------|--------------------------------|
|                        | No. (%)\(^a\) | aOR\(^b\) (95% CI) | \(P\) | No. (%)\(^a\) | aOR\(^b\) (95% CI) | \(P\) | No. (%)\(^a\) |
| Anxiety, HADS          |                  |                         |      |                  |                         |      |                      |
| Borderline or case     | 703 (79.0)       | 1.32 (0.97 to 1.82)    | .0988 | 508 (64.0)       | 1.22 (0.96 to 1.55)    | .059  | 1,310 (52.6)          |
| Normal                 | 187 (21.0)       | Ref                    |      | 286 (36.0)       | Ref                    |      | 1,179 (47.4)          |
| Depression, HADS       |                  |                         | <.001 |                  |                         |      |                      |
| Borderline or case     | 377 (42.4)       | 3.89 (2.79 to 5.41)    | <.001 | 138 (17.4)       | 1.42 (0.97 to 2.07)    | <.001 | 228 (9.2)             |
| Normal                 | 513 (57.6)       | Ref                    |      | 656 (82.6)       | Ref                    |      | 2,261 (90.8)          |
| Pain score, EORTC C30, continuous, mean ± SD | 35.1 ± 27.6 | 1.07 (1.06 to 1.08) | <.001 | 17.9 ± 19.5 | 1.03 (1.02 to 1.04) < .001 | 7.9 ± 13.3 |
| Insomnia score, EORTC C30, continuous, mean ± SD | 67.9 ± 33.0 | 1.03 (1.02 to 1.03) | <.001 | 43.2 ± 31.7 | 1.01 (1.00 to 1.01) < .001 | 33.6 ± 28.9 |
| Hot flashes            |                  |                         | 0.957 |                  |                         |      |                      |
| Yes                    | 254 (28.5)       | 1.02 (0.76 to 1.37)    | <.001 | 263 (33.1)       | 1.33 (1.04 to 1.71)    | <.001 | 647 (26.0)            |
| No                     | 636 (71.5)       | Ref                    |      | 531 (66.9)       | Ref                    |      | 1,842 (74.0)          |

NOTE. Scores ≥ 40 of 100 defined as severe fatigue. Abbreviations: aOR, adjusted odds ratio; BC, breast cancer; BMI, body mass index; EORTC, European Organisation for Research and Treatment of Cancer; GPAQ16, Global Physical Activity Questionnaire-16; HADS, Hospital Anxiety and Depression Scale; HER2, human epidermal growth factor receptor 2; Q, quartile; SD, standard deviation.

\(^a\)Values are No. (%) unless otherwise stated.

\(^b\)Models are adjusted for all the factors in the table.

DISCUSSION

This study highlights the multidimensional nature of cancer-related fatigue and the complexity of its risk factors that include both common and dimension-specific determinants. The distinct dimensions of fatigue that we examined presented different longitudinal patterns and were differentially affected by multiple factors, including classical sociodemographic and clinical factors and treatment-related factors. Common determinants of trajectory membership were found, including emotional distress—particularly depression—that emerged as the most potent driver of fatigue trajectory, independent of the explored dimension. Receipt of systemic treatments—particularly hormonal therapy—was a consistent risk factor for developing severe fatigue and clearly isolated groups of patients with deteriorating fatigue symptoms compared with those at low risk of fatigue, across different dimensions of the symptom.

More than 50% of cancer survivors suffer from at least one severe post-treatment symptom, calling for an improved survivorship care model that focuses on managing long-term and late effects of treatment.\(^{25}\) Substantial evidence shows that long and late effects of cancer treatment are often underaddressed.\(^{24}\) Therefore, in recent years, the concept of personalized survivorship care has emerged. This concept implies patient stratification on the basis of understanding longitudinal determinants of long-term and late effects and the development of appropriate care pathways to allow tailored care.\(^{25}\) In this setting, our study focused on performing an extensive characterization of the patterns of one of the most prevalent and distressing symptoms after a BC diagnosis and cancer-related fatigue and on informing risk stratification that is clinically actionable.

Previous literature has suggested that the patient population that is at higher risk of cancer-related fatigue includes (1) those who are more fragile at the time of diagnosis, including being young, belonging to lower socioeconomic class, not partnered, having higher BMI, comorbidities, being a smoker, presenting heavier psychologic distress (depressive and anxiety symptoms), and concomitant symptom burden and (2) those who receive specific classes of treatment such as chemotherapy and endocrine therapy.\(^{4-9,26}\) Some previous studies have suggested that there are clusters of patients who experience distinct trajectories of fatigue.\(^{27}\) For example, Bower et al examined post-treatment fatigue trajectories in 191 women with early-stage BC. This cohort\(^{15}\) had a follow-up time of 4.3 years after treatment and identified four distinct patterns of fatigue after BC: (1) low fatigue group (44%), where patients presented low fatigue levels throughout the duration of the observation; (2) recovery group (28%), where patients were fatigued at the initial post-treatment assessment but then recovered their energy levels; (3) \(late\)
| Patient Characteristic | Group A: High (n = 533 [13%]) | Group B: Deteriorating (n = 940 [23%]) | Group C: Recovery (n = 476 [11%]) | Group D: Low (n = 2,224 [53%]) |
|-------------------------|-------------------------------|---------------------------------------|----------------------------------|----------------------------------|
| Age, continuous (1-year increase), mean ± SD | 55.2 ± 11.4 | 0.97 (0.95 to 0.99) | .001 | 54.3 ± 11.4 | 0.98 (0.97 to 0.99) | < .001 | 51.4 ± 11.8 | 0.95 (0.93 to 0.97) | < .001 | 56.7 ± 10.8 |
| BMI, continuous, mean ± SD | 27.1 ± 5.9 | 1.08 (1.04 to 1.11) | < .001 | 26.1 ± 5.4 | 1.05 (1.03 to 1.07) | < .001 | 25.9 ± 5.1 | 1.06 (1.02 to 1.10) | < .001 | 25.2 ± 4.9 |
| Physical activity, GPAQ16, continuous, median (Q1-Q3) | 8.0 (0.0-29.0) | 1.00 (1.00 to 1.00) | .1139 | 16.0 (1.7-42.0) | 1.00 (1.00 to 1.00) | .7948 | 12.0 (0.0-42.3) | 1.00 (1.00 to 1.00) | .4608 | 16.0 (4.0-40.0) |
| Smoking behavior | < .001 | .0158 | .049 | .4560 |
| Current or former smoker | 259 (48.6) | 1.58 (1.09 to 2.28) | .001 | 206 (43.1) | 1.15 (0.80 to 1.65) | .001 | 767 (34.5) |
| Never smoker | 274 (51.4) | Ref | 537 (57.1) | Ref | 271 (56.9) | Ref | 1,457 (65.5) |
| Charlson | < .001 | .0304 | .1027 |
| ≥ 1 | 161 (30.2) | 2.16 (1.40 to 3.33) | .001 | 197 (21.0) | 1.36 (1.03 to 1.79) | .001 | 90 (18.9) | 1.47 (0.93 to 2.33) | .001 | 366 (16.5) |
| 0 | 372 (69.8) | Ref | 743 (79.0) | Ref | 386 (81.1) | Ref | 1,858 (83.5) |
| Marital status | .003 | .0755 | .0181 |
| Not partnered | 200 (37.5) | 1.97 (1.26 to 3.09) | .003 | 270 (28.7) | 1.27 (0.98 to 1.67) | .003 | 123 (25.8) | 1.73 (1.10 to 2.72) | .003 | 545 (24.5) |
| Partnered | 333 (62.5) | Ref | 670 (71.3) | Ref | 353 (74.2) | Ref | 1,679 (75.5) |
| Degree level | .3319 | .2991 | .7737 |
| High school or higher | 451 (84.6) | 1.33 (0.75 to 2.36) | .3319 | 823 (87.6) | 1.20 (0.85 to 1.70) | .3319 | 425 (89.3) | 1.09 (0.59 to 2.03) | .3319 | 1,918 (86.2) |
| Primary school | 82 (15.4) | Ref | 117 (12.4) | Ref | 51 (10.7) | Ref | 306 (13.8) |
| Income, Euro/month | .0989 | .0512 | .4191 |
| ≥ 3,000 | 155 (29.1) | 1.42 (0.94 to 2.15) | .0989 | 386 (41.1) | 1.27 (1.00 to 1.62) | .0989 | 236 (49.6) | 0.85 (0.57 to 1.26) | .0989 | 1,100 (49.5) |
| < 3,000 | 378 (70.9) | Ref | 554 (58.9) | Ref | 240 (50.4) | Ref | 1,124 (50.5) |
| BC stage | .3799 | .8466 | .1165 |
| II/III | 295 (55.3) | 1.24 (0.77 to 1.99) | .3799 | 498 (53.0) | 0.97 (0.74 to 1.28) | .3799 | 295 (54.4) | 1.44 (0.91 to 2.29) | .3799 | 1,045 (47.0) |
| I | 238 (44.7) | Ref | 442 (47.0) | Ref | 217 (45.6) | Ref | 1,179 (53.0) |
| BC surgery | .6194 | .5479 | .1222 |
| Mastectomy | 146 (27.4) | 1.14 (0.68 to 1.89) | .6194 | 265 (28.2) | 1.09 (0.82 to 1.47) | .6194 | 161 (33.8) | 1.45 (0.90 to 2.33) | .6194 | 541 (24.3) |
| Partial breast surgery | 387 (72.6) | Ref | 675 (71.8) | Ref | 315 (66.2) | Ref | 1,683 (75.7) |
| Axillary surgery | .1768 | .6627 | .1131 |
| Axillary dissection | 222 (41.7) | 0.71 (0.43 to 1.17) | .1768 | 423 (45.0) | 1.06 (0.80 to 1.41) | .1768 | 195 (41.0) | 0.67 (0.41 to 1.10) | .1768 | 829 (37.3) |
| Sentinel node | 311 (58.3) | Ref | 517 (55.0) | Ref | 281 (59.0) | Ref | 1,395 (62.7) |

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**TABLE 2.** Distribution of Patient Characteristics at Diagnosis and Breast Cancer Primary Treatment by Severe Physical Trajectory Group and Multinomial Logistic Regression (n reference group D: low, n = 2,224 [53%]) (continued)

| Patient Characteristic | Group A: High (n = 533 [13%]) | Group B: Deteriorating (n = 940 [23%]) | Group C: Recovery (n = 476 [11%]) | Group D: Low (n = 2,224 [53%]) |
|------------------------|------------------|------------------|------------------|------------------|
|                        | No. (%) | aOR (95% Cl) | P       | No. (%) | aOR (95% Cl) | P       | No. (%) | aOR (95% Cl) | P       | No. (%) | aOR (95% Cl) | P       |
| Radiation therapy      |         |              |         |         |              |         |         |              |         |         |              |         |
| Yes                   | 485 (91.0) | 1.01 (0.51 to 2.02) | .9779  | 879 (93.5) | 1.34 (0.85 to 2.12) | .2039  | 427 (89.7) | 1.12 (0.59 to 2.13) | .7368  | 2,018 (90.7) | Ref    |
| No                    | 48 (9.0) | Ref |         | 61 (6.5) | Ref |         | 49 (10.3) | Ref |         | 206 (9.3) | Ref |
| Chemotherapy           |         |              |         |         |              |         |         |              |         |         |              |         |
| Yes                   | 307 (57.6) | 0.89 (0.55 to 1.43) | .6257  | 571 (60.7) | 1.17 (0.89 to 1.55) | .2631  | 263 (55.3) | 0.59 (0.36 to 0.95) | .0284  | 1,127 (50.7) | Ref    |
| No                    | 226 (42.4) | Ref |         | 369 (39.3) | Ref |         | 213 (44.7) | Ref |         | 1,097 (49.3) | Ref |
| Hormonal therapy       |         |              |         |         |              |         |         |              |         |         |              |         |
| Yes                   | 425 (79.7) | 1.12 (0.70 to 1.79) | .6490  | 803 (85.4) | 1.53 (1.13 to 2.06) | .005   | 379 (79.6) | 1.06 (0.67 to 1.67) | .7939  | 1,781 (80.1) | Ref    |
| No                    | 108 (20.3) | Ref |         | 137 (14.6) | Ref |         | 97 (20.4) | Ref |         | 443 (19.9) | Ref |
| Anti-HER2 therapy      |         |              |         |         |              |         |         |              |         |         |              |         |
| Yes                   | 48 (9.0) | 0.69 (0.34 to 1.40) | .3040  | 141 (15.0) | 1.18 (0.85 to 1.64) | .3249  | 76 (16.0) | 1.23 (0.72 to 2.12) | .4500  | 247 (11.1) | Ref    |
| No                    | 485 (91.0) | Ref |         | 799 (85.0) | Ref |         | 400 (84.0) | Ref |         | 1,977 (88.9) | Ref |
| Anxiety, HADS          |         |              |         |         |              |         |         |              |         |         |              |         |
| Borderline or case     | 451 (84.6) | 2.33 (1.42 to 3.81) | < .001 | 582 (61.9) | 1.30 (1.04 to 1.63) | .0233  | 400 (84.0) | 2.40 (1.52 to 3.77) | < .001 | 1,088 (48.9) | Ref    |
| Normal                 | 82 (15.4) | Ref |         | 358 (38.1) | Ref |         | 76 (16.0) | Ref |         | 1,136 (51.1) | Ref |
| Depression, HADS       |         |              |         |         |              |         |         |              |         |         |              |         |
| Borderline or case     | 322 (60.4) | 23.19 (11.89 to 45.21) | < .001 | 105 (11.2) | 2.40 (1.49 to 3.87) | < .001 | 215 (45.2) | 9.95 (5.56 to 17.78) | < .001 | 101 (4.5) | Ref    |
| Normal                 | 211 (39.6) | Ref |         | 835 (88.8) | Ref |         | 261 (54.8) | Ref |         | 3,213 (95.5) | Ref |
| Pain score, EORTC C30, continuous, mean ± SD | 40.7 ± 27.9 | 1.08 (1.06 to 1.09) | < .001 | 15.1 ± 17.7 | 1.03 (1.02 to 1.04) | < .001 | 26.5 ± 25.4 | 1.06 (1.04 to 1.07) | < .001 | 7.4 ± 12.6 | Ref    |
| Insomnia score, EORTC C30, continuous, mean ± SD | 66.4 ± 34.0 | 1.02 (1.02 to 1.03) | < .001 | 44.5 ± 32.5 | 1.01 (1.01 to 1.02) | < .001 | 64.1 ± 32.7 | 1.02 (1.02 to 1.03) | < .001 | 31.8 ± 27.8 | Ref    |
| Hot flashes            |         |              |         |         |              |         |         |              |         |         |              |         |
| Yes                   | 191 (35.8) | 1.29 (0.87 to 1.92) | .2035  | 272 (28.9) | 1.06 (0.83 to 1.35) | .6544  | 119 (25.0) | 0.95 (0.63 to 1.43) | .8004  | 582 (26.2) | Ref    |
| No                    | 342 (64.2) | Ref |         | 668 (81.1) | Ref |         | 357 (75.0) | Ref |         | 1,642 (73.8) | Ref |

NOTE. Scores ≥ 40 of 100 defined as severe fatigue. Abbreviations: aOR, adjusted odds ratio; BC, breast cancer; BMI, body mass index; EORTC, European Organisation for Research and Treatment of Cancer; GPAQ16, Global Physical Activity Questionnaire-16; HADS, Hospital Anxiety and Depression Scale; HER2, human epidermal growth factor receptor 2; Q, quartile; SD, standard deviation.

Values are No. (%) unless otherwise stated.

Models are adjusted for all the factors in the table.
oup (17%) where patients presented with low post-treatment levels of fatigue but then gradually started to report increased fatigue levels over time; and (4) high fatigue group (11%), where fatigue was persistently elevated across the study period. In this study, psychologic factors, such as depressive symptoms and childhood adversity, were the strongest predictors of membership in high and recovery groups. Furthermore, there was a suggestion that treatment factors played a role in fatigue trajectories, with chemotherapy being associated with membership to the recovery group and endocrine therapy contributing to the fatigue observed in the high group.15 Recently, the same authors identified consistent trajectories among 270 BC survivors, defining five fatigue groups: stable low (66%), stable high (13%), decreasing (4%), increasing (9%), and reactive (8%).28 Our study confirms and expands on these previous studies. Particularly, our study calls for the implementation of several actions in the clinical care of patients with BC.

First, by describing consistent and consolidated variables associated with worse trajectories of cancer-related fatigue, our data can assist clinicians to focus on relevant patient characteristics that are consistently associated with long-term patterns of severe fatigue. These variables include age, BMI, tobacco use, receipt of hormonal therapy, and concomitant symptom burden (pain, insomnia, and depression). An accurate and systematic screening of cancer-related fatigue and associated risk factors—at diagnosis and over the survivorship period—can therefore help in the identification of the most vulnerable.

Second, by stressing that several of the cancer-related fatigue risk factors are modifiable, this study advocates for the implementation of symptom management and health promotion strategies since diagnosis. Strategies addressing modifiable risk factors include healthy weight management, smoking cessation, and cognitive-behavioral therapy for concomitant symptoms such as sleep disturbances and emotional distress, or specific treatment of chronic pain, which should be considered early in the patient journey. In addition, there are patients whose fatigue trajectory is characterized by high levels of pretreatment fatigue, and therefore, they deserve the upfront implementation of strategies to mitigate this symptom since the moment of diagnosis. This is particularly relevant considering that fatigue is probably only one of the outcomes of cancer-related accelerating aging that can be affected by these modifiable host-specific factors.29

Third, our study findings are provocative in that not all the dimensions of cancer-related fatigue seem to have the same longitudinal evolution and determinants. Depending on the dimension, an interaction between treatment exposures and host vulnerabilities such as psychologic factors, sociodemographic factors such as age and loneliness, and clinical features such as comorbidities can promote and render fatigue more persistent in cancer survivors. This calls for a comprehensive evaluation at diagnosis and with attention to examination of risk factors in light of their dimension-specific effect.

Our study advocates for a systematic pretreatment screening for fatigue and risk factors among patients newly diagnosed with BC and for the implementation of a proactive management of cancer-related fatigue and risk factors over the course of the survivorship period. In addition, efforts should be made to truly transform the survivorship journey in a fully patient-centered model, by promoting patient participation in the process of care, through increased awareness and education and interdisciplinary referral and access to interventions to better manage survivorship-related issues including long-term symptom management. Particularly, patients should be educated to self-monitor changes in fatigue levels over time, encouraged to be attentive to symptoms that can herald the onset of persistent fatigue, and advised to seek medical help if a persistent deterioration of energy levels exists (Fig 2).32-35

Finally, by highlighting the complexity of post-treatment symptom patterns, this study also offers insight into multiple challenges that are ahead of the implementation of a survivorship model aiming to deliver comprehensive, patient-centered survivorship care. One of these challenges is the need of scalable models, which is a particularly relevant topic in an era of oncology workforce shortage and professional burnout.36,37 Relying on digital solutions may facilitate the uptake of personalized care models in diverse settings. The use of electronic monitoring to understand post-treatment trajectories and promote patient care holds the promise to lead to greater awareness and better management of treatment-related symptoms.38,39 Telemedicine self-management programs showed promising results on prevalent symptoms of cancer survivors.40-47

We acknowledge several limitations of this study. First, CANTO is a longitudinal study with the common limitation of increasing response attrition the further away from study entry. Therefore, we acknowledge potential for selection and attrition bias over time. However, GBTM can accommodate missing outcome data, and sensitivity analyses trying to address these points confirmed the robustness of our findings.20 Second, there are some well-known determinants of fatigue that could not be explored, including psychologic measures such as childhood adversity and biologic markers such as inflammatory cytokines.9,15 Third, our population only included French survivors, and results may not be fully generalizable, but still included patients from across the country. As lower-income/less-educated and older patients, other subpopulations might be underrepresented in this study, warranting a dedicated approach in future studies. Fourth, we included a population diagnosed between 2012 and 2015, and treatment practices have slightly changed since. Fifth, because of the observational design, we cannot exclude unmeasured confounding and no formal adjustment for multiplicity has been performed given the exploratory modeling. Finally, the
### TABLE 3. Distribution of Patient Characteristics at Diagnosis and Breast Cancer Primary Treatment by Severe Emotional Trajectory Group (n reference group C: recovery, n = 631 [15%])

| Patient Characteristic | Group A: High (n = 400 [10%]) | Group B: Deteriorating (n = 807 [19%]) | Group C: Recovery (n = 631 [15%]) | Group D: Low (n = 2,335 [56%]) |
|------------------------|---------------------------------|-------------------------------------|----------------------------------|--------------------------------|
| Age, continuous (1-year increase), mean ± SD | 54.4 ± 10.8 | 53.8 ± 11.1 | 53.1 ± 11.2 | 56.7 ± 11.2 |
| BMI, continuous, mean ± SD | 26.8 ± 5.8 | 25.9 ± 5.3 | 25.2 ± 5.3 | 25.6 ± 5.3 |
| Physical activity, GPAQ16, median (Q1-Q3) | 10.0 (0.0-41.0) | 14.0 (1.0-43.7) | 14.0 (0.0-42.0) | 16.0 (3.0-37.0) |
| Smoking behavior | .0135 | .0075 | .1365 | 1.365 |
| Current or former smoker | 193 (48.3) | 393 (48.7) | 233 (36.9) | 815 (34.9) |
| Never smoker | 207 (51.8) | 414 (51.3) | 398 (63.1) | 1,520 (65.1) |
| Charlson | .6015 | .7743 | .8627 | .8627 |
| ≥ 1 | 97 (24.3) | 174 (21.6) | 110 (17.4) | 433 (18.5) |
| 0 | 303 (75.8) | 633 (78.4) | 521 (82.6) | 1,902 (81.5) |
| Marital status | .5160 | .6687 | .2063 | .2063 |
| Not partnered | 283 (70.8) | 520 (64.4) | 478 (75.8) | 1,754 (75.1) |
| Partnered | 117 (29.3) | 287 (35.6) | 153 (24.2) | 581 (24.9) |
| Degree level | .9289 | .9476 | .8590 | .8590 |
| High school or higher | 66 (16.5) | 103 (12.8) | 69 (10.9) | 318 (13.6) |
| Primary school | 334 (83.5) | 704 (87.2) | 562 (89.1) | 2,017 (86.4) |
| Income, Euro/month | .0046 | .0132 | .0514 | .0514 |
| ≥ 3,000 | 129 (32.3) | 291 (36.1) | 333 (52.8) | 1,124 (48.1) |
| < 3,000 | 271 (67.8) | 516 (63.9) | 298 (47.2) | 1,211 (51.9) |
| BC stage | .7219 | .6895 | .4332 | .4332 |
| II/III | 220 (55.0) | 458 (56.8) | 328 (52.0) | 1,091 (46.7) |
| I | 180 (45.0) | 349 (43.2) | 303 (48.0) | 1,244 (53.3) |
| BC surgery | .9830 | .0193 | .0109 | .0109 |
| Mastectomy | 123 (30.8) | 222 (27.5) | 215 (34.1) | 553 (23.7) |
| Partial breast surgery | 277 (69.3) | 585 (72.5) | 416 (65.9) | 1,782 (76.3) |
| Axillary surgery | .8159 | .1514 | .2803 | .2803 |
| Axillary dissection | 174 (43.5) | 379 (47.0) | 260 (41.2) | 856 (36.7) |
| Sentinel node | 226 (56.5) | 428 (53.0) | 371 (58.8) | 1,479 (63.3) |
| Radiation therapy | .2654 | .2738 | .3347 | .3347 |
| Yes | 373 (93.3) | 737 (91.3) | 561 (88.9) | 2,138 (91.6) |
| No | 27 (6.8) | 70 (8.7) | 70 (11.1) | 197 (8.4) |

(continued on following page)
### TABLE 3. Distribution of Patient Characteristics at Diagnosis and Breast Cancer Primary Treatment by Severe Emotional Trajectory Group (v reference group C: recovery, n = 631 [15%]) (continued)

| Patient Characteristic | Group A: High (n = 400 [10%]) | Group B: Deteriorating (n = 807 [19%]) | Group C: Recovery (n = 631 [15%]) | Group D: Low (n = 2,335 [56%]) |
|------------------------|--------------------------------|--------------------------------------|----------------------------------|--------------------------------|
|                        | No. (%) * aOR (95% CI)        | No. (%) * aOR (95% CI)                | No. (%) * aOR (95% CI)            | No. (%) * aOR (95% CI)          |
| Chemotherapy           | .8298 .0697                   | .2243                                |                                  |                                |
| Yes                   | 231 (57.8) 1.05 (0.65 to 1.71) | 512 (63.4) 1.77 (0.96 to 3.27)       | 360 (57.1) 1.165 (49.9) 1.41 (0.81 to 2.44) |                                |
| No                    | 169 (42.3) Ref                | 295 (36.6) Ref                       | 271 (42.9) 1.170 (50.1) Ref      |                                |
| Hormonal therapy      | .3738 .1385                   | .9367                                |                                  |                                |
| Yes                   | 309 (77.3) 0.80 (0.49 to 1.31) | 696 (86.2) 1.64 (0.85 to 3.15)       | 510 (80.8) 1.873 (80.2) 0.98 (0.56 to 1.71) |                                |
| No                    | 91 (22.8) Ref                | 111 (13.8) Ref                       | 121 (19.2) 462 (19.8) Ref       |                                |
| Anti-HER2 therapy     | .3321 .1880                   | .0489                                |                                  |                                |
| Yes                   | 48 (12.0) 0.75 (0.41 to 1.35) | 116 (14.4) 0.62 (0.30 to 1.27)       | 106 (16.8) 242 (10.4) 0.52 (0.27 to 1.00) |                                |
| No                    | 352 (88.0) Ref                | 691 (85.6) Ref                       | 525 (83.2) 2,093 (89.6) Ref     |                                |
| Anxiety, HADS         | .0000 .0000                   | .8204                                |                                  |                                |
| Borderline or case    | 394 (98.5) 0.04 (0.01 to 0.12) | 508 (62.9) 0.08 (0.03 to 0.26)       | 620 (98.3) 999 (42.8) 1.18 (0.27 to 5.11) |                                |
| Normal                | 6 (1.5) Ref                   | 299 (37.1) Ref                       | 11 (1.7) 1,336 (57.2) Ref       |                                |
| Depression, HADS      | .0000 .0000                   | .0002                                |                                  |                                |
| Borderline or case    | 315 (78.8) 0.03 (0.01 to 0.13) | 61 (7.6) 0.15 (0.07 to 0.33)         | 338 (53.6) 29 (1.2) 2.81 (1.62 to 4.88) |                                |
| Normal                | 85 (21.3) Ref                 | 746 (92.4) Ref                       | 293 (46.4) 2,306 (98.8) Ref     |                                |
| Pain score, EORTC C30, continuous, mean ± SD | 35.7 ± 28.8 0.98 (0.97 to 0.99) .0001 | 21.4 ± 23.4 1.00 (0.99 to 1.02) .4568 | 18.3 ± 22.2 9.4 ± 15.3 1.02 (1.01 to 1.03) .0000 |                                |
| Insomnia score, EORTC C30, continuous, mean ± SD | 70.6 ± 32.6 0.98 (0.97 to 0.98) .0000 | 46.8 ± 32.7 0.99 (0.98 to 1.00) .0037 | 60.7 ± 32.9 31.7 ± 28.1 1.01 (1.00 to 1.01) .1089 |                                |
| Hot flashes           | .5939 .1755                   | .0742                                |                                  |                                |
| Yes                   | 145 (36.3) 1.14 (0.70 to 1.87) | 260 (32.2) 1.45 (0.85 to 2.50)       | 151 (23.9) 608 (26.0) 1.47 (0.96 to 2.26) |                                |
| No                    | 255 (63.8) Ref                | 547 (67.8) Ref                       | 480 (76.1) 1,727 (74.0) Ref     |                                |

Note. Scores ≥ 40 of 100 defined as severe fatigue.

Abbreviations: aOR, adjusted odds ratio; BC, breast cancer; BMI, body mass index; EORTC, European Organisation for Research and Treatment of Cancer; GPAQ16, Global Physical Activity Questionnaire-16; HADS, Hospital Anxiety and Depression Scale; HER2, human epidermal growth factor receptor 2; Q, quartile; SD, standard deviation.

*Values are No. (%) unless otherwise stated.

'Models are adjusted for all the factors in the table.'
### TABLE 4. Distribution of Patient Characteristics at Diagnosis and Breast Cancer Primary Treatment by Severe Cognitive Fatigue Trajectory Group and Multinomial Logistic Regression Membership (v reference group B: low, n = 3,288 [79%])

| Patient Characteristic | Cognitive Fatigue FA12 | Group A: High (n = 885 [21%]) | Group B: Low (n = 3,288 [79%]) | aOR* (95% CI) | P      | No. (%)* |
|------------------------|------------------------|-------------------------------|---------------------------------|---------------|--------|---------|
| Age, continuous (1-year increase), mean ± SD | 52.2 ± 11.0 | 0.97 (0.95 to 0.98) | < .001 | 56.2 ± 11.2 |
| BMI, continuous, mean ± SD | 26.0 ± 5.5 | 1.01 (0.99 to 1.03) | .372 | 25.6 ± 5.3 |
| Physical activity, continuous, median (Q1-Q3) | 12.0 (0.0-42.0) | 1.00 (1.00 to 1.00) | .175 | 16.0 (2.0-39.0) |
| Smoking behavior | | | | .0114 |
| Current or former smoker | | | | 1.36 (1.07 to 1.72) |
| Never smoker | | | | Ref |
| Charlson $\geq 1$ | 194 (21.9) | 1.09 (0.82 to 1.47) | .337 | 620 (18.9) |
| Charlson 0 | 691 (78.1) | Ref | 2,668 (81.1) |
| Marital status | | | | .0067 |
| Not partnered | 279 (31.5) | 1.29 (0.97 to 1.72) | 1.199 (25.6) |
| Partnered | 606 (68.5) | Ref | 2,429 (73.9) |
| Degree level | | | | .0248 |
| High school or higher | 752 (85.0) | 1.31 (1.00 to 1.71) | 3,000 | 1,567 (47.7) |
| Primary school | 183 (15.0) | Ref | 423 (12.9) |
| Income, Euro/month | | | | .0465 |
| $\geq$ 3,000 | 310 (35.0) | 1.31 (1.00 to 1.71) | 1,567 (47.7) |
| < 3,000 | 575 (65.0) | Ref | 1,721 (52.3) |
| BC stage | | | | .373 |
| II/III | 514 (58.1) | 1.14 (0.85 to 1.54) | 1,583 (48.1) |
| I | 371 (41.9) | Ref | 1,705 (51.9) |
| BC surgery | | | | .0290 |
| Mastectomy | 311 (35.1) | 1.41 (1.04 to 1.93) | 802 (24.4) |
| Partial breast surgery | 574 (64.9) | Ref | 2,486 (75.6) |
| Axillary surgery | | | | .9980 |
| Axillary dissection | 425 (48.0) | 1.0 (0.74 to 1.35) | 1,244 (37.8) |
| Sentinel node | 460 (52.0) | Ref | 2,044 (62.2) |
| Radiation therapy | | | | .8248 |
| Yes | 798 (90.2) | 1.05 (0.67 to 1.66) | 3,011 (91.6) |
| No | 87 (9.8) | Ref | 277 (8.4) |
| Chemotherapy | | | | .6178 |
| Yes | 563 (63.6) | 1.08 (0.80 to 1.46) | 1,705 (51.9) |
| No | 322 (36.4) | Ref | 1,583 (48.1) |
| Hormonal therapy | | | | .3063 |
| Yes | 717 (81.0) | 1.17 (0.87 to 1.59) | 2,671 (81.2) |
| No | 168 (19.0) | Ref | 617 (18.8) |
| Anti-HER2 therapy | | | | .5526 |
| Yes | 130 (14.7) | 1.11 (0.78 to 1.59) | 382 (11.6) |
| No | 755 (85.3) | Ref | 2,906 (88.4) |

(continued on following page)
risk models for belonging to particular trajectory groups may underestimate the uncertainty obtained from the trajectory modeling in the first stage.

In conclusion, this study provides insight into the long-term evolution and fluctuation of fatigue symptomatology that may arise from chronic illnesses other than malignancies and offers an actionable clinical perspective. Identifying key risk factors and underlying mechanisms is critical for developing and deploying targeted interventions to reduce the burden of long-term effects from cancer and its treatment, including fatigue.

**TABLE 4.** Distribution of Patient Characteristics at Diagnosis and Breast Cancer Primary Treatment by Severe Cognitive Fatigue Trajectory Group and Multinomial Logistic Regression Membership (v reference group B: low, n = 3,288 [79%]) (continued)

| Cognitive Fatigue FA12 | Group A: High (n = 885 [21%]) | Group B: Low (n = 3,288 [79%]) |
|------------------------|-------------------------------|-------------------------------|
| **Patient Characteristic** | **No. (%)*** | **aOR** (95% CI) | **P** | **No. (%)*** |
| Anxiety, HADS | | | | |
| Borderline or case | 779 (88.0) | 2.46 (1.83 to 3.30) | < .001 | 1,742 (53.0) |
| Normal | 106 (12.0) | Ref | 1,546 (47.0) |
| Depression, HADS | | | < .001 | |
| Borderline or case | 459 (51.9) | 5.74 (4.36 to 7.55) | 284 (8.6) |
| Normal | 426 (48.1) | Ref | 3,004 (91.4) |
| Pain score, EORTC C30, continuous, mean ± SD | 28.2 ± 27.3 | 1.02 (1.01 to 1.02) | < .001 | 12.2 ± 18.1 |
| Insomnia score, EORTC C30, continuous, mean ± SD | 62.5 ± 34.5 | 1.01 (1.01 to 1.01) | < .001 | 37.5 ± 30.9 |
| Hot flashes | | 1.02 (1.01 to 1.02) | < .001 | 1.01 (1.01 to 1.01) | < .001 |
| Yes | 273 (30.8) | 1.17 (0.91 to 1.51) | 37.5 ± 30.9 | 891 (27.1) |
| No | 612 (69.2) | Ref | 2,397 (72.9) |

**NOTE.** Scores ≥ 40 of 100 defined as severe fatigue. Abbreviations: aOR, adjusted odds ratio; BC, breast cancer; BMI, body mass index; EORTC, European Organisation for Research and Treatment of Cancer; GPAQ16, Global Physical Activity Questionnaire-16; HADS, Hospital Anxiety and Depression Scale; HER2, human epidermal growth factor receptor 2; Q, quartile; SD, standard deviation.

*Values are No. (%) unless otherwise stated.

*Models are adjusted for all the factors in the table.

**FIG 2.** A comprehensive patient-centered survivorship care model building on predicted longitudinal symptom patterns to avoid long-term deterioration. BMI, body mass index.
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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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DATA SHARING STATEMENT
Data will be available upon request to Unicancer R&D.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Long-Term Longitudinal Patterns of Patient-Reported Fatigue After Breast Cancer: A Group-Based Trajectory Analysis

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