original reports

Dynamics of Long-Term Patient-Reported Quality of Life and Health Behaviors After Adjuvant Breast Cancer Chemotherapy

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abstract

PURPOSE We aimed to characterize long-term quality of life (QOL) trajectories among patients with breast cancer treated with adjuvant chemotherapy and to identify related patterns of health behaviors.

METHODS Female stage I-III breast cancer patients receiving chemotherapy in CANTO (CANcer TOxicity; ClinicalTrials.gov identifier: NCT01993498) were included. Trajectories of QOL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–C30 Summary Score) and associations with trajectory group membership were identified by iterative estimations of group-based trajectory models and multivariable multinomial logistic regression, respectively.

RESULTS Four trajectory groups were identified (N = 4,131): excellent (51.7%), very good (31.7%), deteriorating (10.0%), and poor (6.6%) QOL. The deteriorating trajectory group reported fairly good baseline QOL (mean [95% CI], 78.3/100 [76.2 to 80.5]), which significantly worsened at year-1 (58.1/100 [56.4 to 59.9]) and never recovered to pretreatment values through year-4 (61.1/100 [59.0 to 63.3]) postdiagnosis. Healthy behaviors were associated with better performing trajectory groups. Obesity (adjusted odds ratio [aOR] *v* lean, 1.51 [95% CI, 1.28 to 1.79]; $P < .0001$) and current smoking (aOR *v* never, 1.52 [95% CI, 1.27 to 1.82]; $P < .0001$) at diagnosis were associated with membership to the deteriorating group, which was also characterized by a higher prevalence of patients with excess body weight and insufficient physical activity through year-4 and by frequent exposure to tobacco smoking during chemotherapy. Additional factors associated with membership to the deteriorating group included younger age (aOR, 1-year decrement 1.01 [95% CI, 1.01 to 1.02]; $P = .043$), comorbidities (aOR *v* no, 1.22 [95% CI, 1.06 to 1.40]; $P = .005$), lower income (aOR *v* wealthier households, 1.21 [95% CI, 1.07 to 1.37]; $P = .002$), and endocrine therapy (aOR *v* no, 1.14 [95% CI, 1.01 to 1.30]; $P = .047$).

CONCLUSION This latent-class analysis identified some patients with upfront poor QOL and a high-risk cluster with severe, persistent postchemotherapy QOL deterioration. Screening relevant patient-level characteristics may inform tailored interventions to mitigate the detrimental impact of chemotherapy and preserve QOL, including early addressal of behavioral concerns and provision of healthy lifestyle support programs.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Survival of patients with breast cancer (BC) has dramatically increased over the past decades, because of earlier diagnosis and advanced treatment.[1-4] Current multimodal risk-reduction strategies, including adjuvant chemotherapy, endocrine therapies, and targeted agents, lead to survival rates exceeding 80% at 10 years after diagnosis of early-stage BC.[5]

Nevertheless, this survival benefit is often associated with relevant late and long-term health-related costs.[6] Downstream effects of adjuvant BC treatments include substantial impact on general well-being, physical functioning, and vitality, and alterations in cognition, metabolism, and sexuality.[7-9] Chemotherapy is associated with poorer emotional and social functioning, body-image issues, increased likelihood of unemployment after cancer, and persisting conditions including fatigue, neuropathy, and menopausal symptoms.[10-13]

Previous research indicates an overall transient negative impact of chemotherapy on quality of life (QOL).[6]

CONTEXT

Key Objective

There is considerable interindividual variability in long-term trajectories of patient-reported quality of life (QOL) after adjuvant breast cancer chemotherapy. We aimed to identify latent clusters of patients at risk for QOL deterioration, and to assess the relationship of host factors and health behaviors with trajectory group membership.

Knowledge Generated

Most patients fared well over time; however, a cluster reported significantly worsened QOL after chemotherapy and never recovered to pretreatment values for up to four years after diagnosis. Excess body weight, physical inactivity, and tobacco exposure were particularly prevalent among this deteriorating QOL trajectory group. Additional risk factors for deteriorated QOL included younger age, comorbidities, lower income, and receipt of endocrine therapy.

Relevance

This study will help identify latent clusters of patients who are at risk of persistent QOL deterioration after chemotherapy and facilitate tailored interventions that may include early addressal of behavioral concerns and provision of healthy lifestyle support programs.

There is, however, considerable interindividual variability in the longitudinal trajectory of patient-reported outcomes (PROs),[14] which may be obscured by a description of the average population level.[15] Few studies comprehensively evaluated PROs beyond the first year after treatment, despite the high prevalence of some symptoms persisting for more than 10 years.[16] Some patient subgroups may follow trajectories at high risk of long-term deterioration in functional health and symptom burden. Data suggest a mediating effect of unhealthy behaviors, such as excess weight, weight gain, and deconditioning, on QOL of post-treatment BC survivors.[17-22] In addition, smokers who continue to do so during cancer treatment have higher odds of severe treatment-related physical or cognitive effects and persistent sleep or mood disturbances.[23-30] Conversely, those who quit are more likely to endure treatments, speed up symptom recovery, and have reduced all-cause mortality.[23,31,32] Frequent alcohol consumption also seems to amplify the risk of adverse health outcomes, including contributing to development of cardiometabolic conditions and obesity.[28,33,34]

Early identification of high-risk groups for QOL deterioration is crucial for timely, patient-specific supportive care interventions, including those facilitating a healthy lifestyle.[35] This study was conducted among women who received adjuvant BC chemotherapy, with the following aims: (1) to describe dynamics of patient-reported QOL over four years after diagnosis of BC; (2) to identify patients at high risk of QOL deterioration; and (3) to focus on how modifiable health behaviors are associated with distinct patterns of QOL over time.

METHODS

Data Source

We used data from CANcer TOxicity (CANTO; ClinicalTrials.gov identifier: NCT01993498), a prospective cohort of women enrolled at the time of diagnosis of stage I-II-III BC, before any treatment. Participants are longitudinally assessed at diagnosis (baseline) and during follow-up visits at year-1, -2, and -4 postdiagnosis. Surgery, chemotherapy, and/or radiation therapy are completed 3-6 months before the year-1 visit. Patients experiencing BC recurrence (other than local), second primary cancers, or death provide data until the time of event, and then exit the study (Data Supplement, online only).[36]

Study Cohort

We included 4,131 patients diagnosed with BC from 2012 to 2015, who received chemotherapy, provided QOL data at diagnosis or during at least one subsequent evaluation, and had potential follow-up reaching year-4 postdiagnosis at the time of analysis (Data Supplement).

Variables of Interest

Outcome variables. Our outcome of interest was the Summary Score of the European Organisation for Research and Treatment of Cancer QOL Questionnaire C30 (range, 0-100). Higher scores indicate better QOL (Data Supplement).[35,37-41]

Exposure variables. We focused on behavior-related variables, available at diagnosis and follow-up time points: (1) clinic-assessed body mass index (BMI), categorized as lean ($\leq$ 24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), or obese ($\geq$ 30.0 kg/m^2)[42]; (2) self-reported physical activity (PA; Global Physical Activity Questionnaire-16), with $\geq$ 10 metabolic equivalents of task-hours/week defining sufficiently active (ie, adhering to WHO recommendations) versus insufficiently active patients ($<$ 10)[43]; (3) tobacco use behavior at diagnosis, categorized as current, former, or never smoker; and (4) alcohol consumption behavior at diagnosis, categorized as daily versus less than daily. Tobacco and alcohol behaviors during follow-up were defined as increased or unchanged versus reduced use, compared with the previous assessment.

TABLE 1. Distribution of Patient Characteristics at Diagnosis by Quality of Life Trajectory Group (N = 4,131)

Characteristic	Excellent (n = 2,134; 51.7%)	Very Good (n = 1,312; 31.7%)	Deteriorating (n = 413; 10.0%)	Poor (n = 272; 6.6%)
Age, years				
Mean (SD)	54.0 (11.4)	52.3 (11.3)	53.1 (9.8)	52.1 (10.6)
Missing	0	0	0	0
BMI, continuous, kg/m^2				
Mean (SD)	25.4 (5.1)	25.8 (5.4)	27.1 (5.9)	26.7 (6.3)
Missing	8	3	1	2
BMI, WHO definition, kg/m^2				
Lean (≤ 24.9)	1,175 (55.3)	679 (51.9)	181 (43.9)	124 (45.9)
Overweight (25.0-29.9)	597 (28.1)	370 (28.3)	116 (28.2)	78 (28.9)
Obese (≥ 30.0)	354 (16.7)	260 (19.9)	115 (27.9)	68 (25.2)
Missing	8	3	1	2
Level of PA, continuous, MET-hours/week				
Total activity, median (Q1-Q3)	14.0 (0.0-36.0)	10.0 (0.0-36.0)	12.0 (0.0-54.0)	9.5 (0.0-50.0)
Transport and leisure-time activity, median (Q1-Q3)	10.0 (0.0-24.0)	6.7 (0.0-20.0)	4.0 (0.0-18.0)	0.3 (0.0-18.7)
Missing	106	67	22	14
Level of PA, WHO definition, MET-hours/week				
Sufficiently active (≥ 10)	1,162 (57.3)	645 (51.8)	223 (57.0)	129 (50.0)
Insufficiently active (< 10)	866 (42.7)	600 (48.2)	168 (43.0)	129 (50.0)
Missing	106	67	22	14
Smoking behavior				
Current smoker	339 (16.1)	260 (20.2)	107 (26.3)	96 (35.4)
Former smoker	471 (22.4)	306 (23.8)	77 (18.9)	53 (19.6)
Never smoker	1,295 (61.5)	721 (56.0)	223 (54.8)	122 (45.0)
Missing	29	25	6	1
Alcohol consumption behavior				
Less than daily	1,785 (86.4)	1,100 (86.4)	347 (86.8)	221 (84.0)
Daily	281 (13.6)	173 (13.6)	53 (13.2)	42 (16.0)
Missing	68	39	13	9
Charlson comorbidity score				
0	1,661 (84.6)	956 (79.2)	286 (76.7)	173 (73.3)
≥ 1	302 (15.4)	251 (20.8)	87 (23.3)	63 (26.7)
Missing	171	105	40	36
Monthly household income, euro				
< 3,000	1,049 (53.3)	703 (57.8)	243 (64.1)	183 (73.2)
≥ 3,000	919 (46.7)	513 (42.2)	136 (35.9)	67 (26.8)
Missing	166	96	34	22
BC stage				
I	564 (26.9)	332 (25.8)	96 (23.5)	60 (22.6)
II	1,184 (56.4)	720 (55.9)	239 (58.6)	150 (56.6)
III	351 (16.7)	235 (18.3)	73 (17.9)	55 (20.8)
Missing	35	25	5	7
BC surgery				
Mastectomy	753 (35.3)	498 (38.0)	158 (38.3)	99 (36.4)

(continued on following page)

TABLE 1. Distribution of Patient Characteristics at Diagnosis by Quality of Life Trajectory Group (N = 4,131) (continued)

Characteristic	Excellent (n = 2,134; 51.7%)	Very Good (n = 1,312; 31.7%)	Deteriorating (n = 413; 10.0%)	Poor (n = 272; 6.6%)
Conservative surgery	1,381 (64.7)	814 (62.0)	255 (61.7)	173 (63.6)
Missing	0	0	0	0
Axillary surgery				
Axillary dissection	1,191 (55.8)	775 (59.1)	259 (62.7)	171 (62.9)
Sentinel node biopsy	943 (44.2)	537 (40.9)	154 (37.3)	101 (37.1)
Missing	0	0	0	0
Radiation therapy				
Yes	1,990 (93.6)	1,221 (93.3)	383 (92.7)	256 (94.1)
No	137 (6.4)	88 (6.7)	30 (7.3)	16 (5.9)
Missing	7	3	0	0
Endocrine therapy				
Yes	1,564 (73.5)	992 (75.8)	325 (78.7)	201 (73.9)
No	564 (26.5)	316 (24.2)	88 (21.3)	71 (26.1)
Missing	6	4	0	0
Anti-HER2 therapy				
Yes	477 (22.4)	296 (22.6)	87 (21.1)	57 (21.0)
No	1,654 (77.6)	1,015 (77.4)	326 (78.9)	215 (79.0)
Missing	3	1	0	0

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviations: BC, breast cancer; BMI, body mass index; HER2, human epidermal growth factor receptor 2; MET, metabolic equivalent of task; PA, physical activity; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

Covariates. These included clinical, socioeconomic, tumor, and treatment characteristics collected at diagnosis (Table 1).

Statistical Analysis

Cohort description. Patient characteristics were descriptively summarized.

Definition of trajectory groups. Longitudinal variations in C30 Summary Score were assessed by Group-Based Trajectory Modeling (GBTM).[44-48] This procedure allowed to define polynomial trajectories and to identify unobserved clusters (latent trajectory groups) of individuals following a similar outcome course. Model selection involved the iterative estimation of the best-fitting (1) number of trajectory groups and (2) shape/order of each trajectory group, tested using maximum likelihood methods. In estimating trajectory groups, time was categorized into years. A detailed description of the model selection procedure is provided in the Data Supplement.

Each identified trajectory group was assigned a label name to provide a brief descriptive representation for the associated QOL outcome pattern. After latent-group identification, we described participant characteristics in each group.

Mean scores for all scales included in the European Organisation for Research and Treatment of Cancer QOL Questionnaire C-30 were summarized by trajectory group, to (1) complement the information provided by the C30 Summary Score, and (2) provide additional granular details on the dynamics of its distinct components.

Trajectory group membership. A weighted multivariable multinomial logistic regression model was subsequently fit to estimate associations between baseline covariates and trajectory group membership. The best pattern of the C30 Summary Score was chosen as reference, in order to focus on factors associated with clustering into groups with worse patterns. To manage missing covariate data, 30 complete-data replicates were obtained using Multivariate Imputation by Chained Equations.[49] The imputation model included all covariates that were part of the analytic model, as well as the outcome and predefined auxiliary variables. The multinomial logistic regression analysis was then applied to each individual imputed data set, and results were combined using Rubin's rules to produce estimates and CIs that incorporate uncertainty of imputed values.[50]

Health behaviors and trajectory groups. Longitudinal measures of BMI, body weight, PA, tobacco, and alcohol behavior were then tabulated and described by trajectory group.

Sensitivity analyses. An extension of GBTM was used to address potential nonrandom participant dropout (eg, truncation because of BC recurrence, second cancer, or death events) that may vary across groups (Data Supplement,

Sensitivity Analysis 1).[51] In addition, analyses were repeated in the overall cohort (n = 4,863, Data Supplement), regardless of a potential follow-up reaching year-4 post-diagnosis (Sensitivity Analysis 2).

Analyses were performed using SAS, v9.4 (including the PROC TRAJ) and R, v4.0.3 (MICE package). Statistical significance was defined with a $P < .05$.

RESULTS

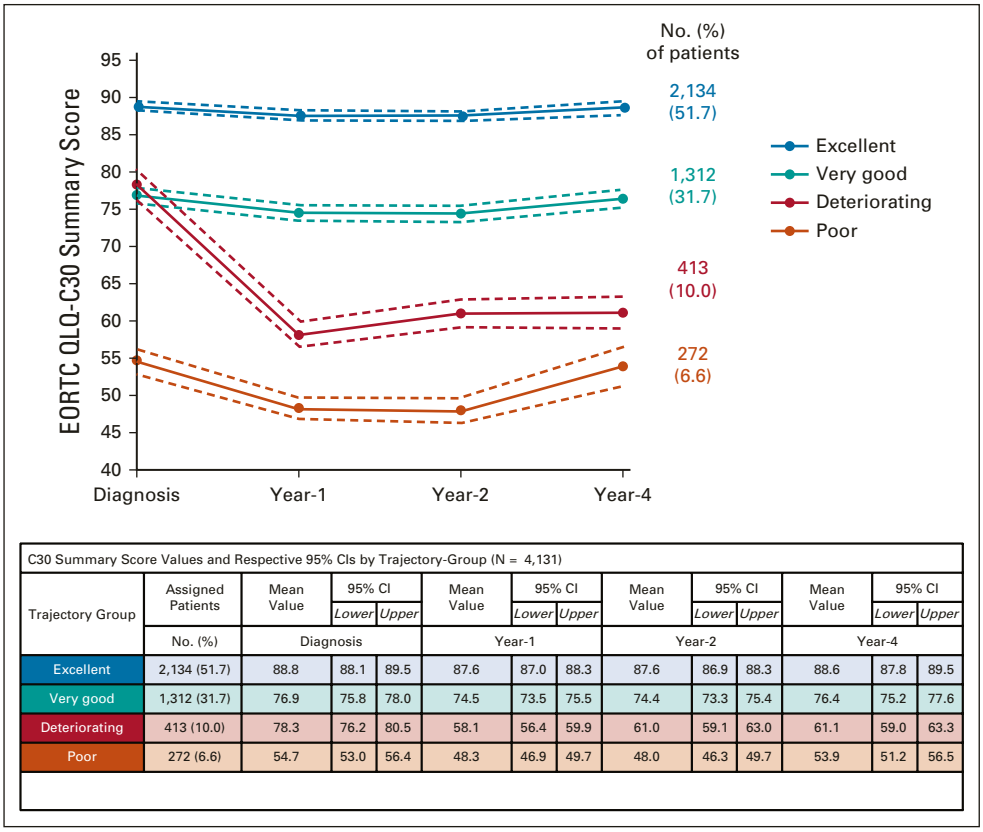
Cohort Characteristics

In the whole cohort (N = 4,131), the mean age was 53.2 years (standard deviation 11.2), 1,161 (28.2%) and 797 (19.4%) patients were overweight and obese, respectively, 1,763 (45.0%) were insufficiently active, 802 (19.7%) current smokers, and 549 (13.3%) consumed alcohol daily (Data Supplement).

QOL Trajectory Groups

Our final model identified four trajectory groups (Fig 1). Model selection metrics are presented in the Data Supplement. The best trajectory group comprised the majority of patients (n = 2,134, 51.7%; excellent), reporting an excellent overtime pattern of C30 Summary Score. The second trajectory group (n = 1,312, 31.7%; very good) fared very well overall, with transient and unremarkable downward inflections in QOL scores at year-1 and year-2. QOL in the third trajectory group (n = 413, 10.0%; deteriorating) was fairly good at diagnosis, with a mean score of 78.3/100 (95% CI, 76.2 to 80.5), similar to the second group, but then declined significantly at 58.1/100 (95% CI, 56.4 to 59.9) at year-1, and recovered only partially at 61.1 (95% CI, 59.0 to 63.3) by year-4. The fourth group (n = 272, 6.6%; poor) reported overall low/very low scores averaging 54.7/100 (53.0 to 56.4) at diagnosis, with some additional downward inflections, then slowly and only partially recovering until year-4.

The deteriorating trajectory group reported mean values crossing the threshold for clinically important functional impairment or symptom severity[52] across multiple QOL domains and experienced the largest mean score changes from diagnosis to year-1 (ie, segment including the chemotherapy treatment portion), showing the greatest



C30 Summary Score Values and Respective 95% CIs by Trajectory-Group (N = 4,131)

Trajectory Group	Assigned Patients	Mean Value	95% CI		Mean Value	95% CI		Mean Value	95% CI		Mean Value	95% CI	
			Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
	No. (%)	Diagnosis			Year-1			Year-2			Year-4		
Excellent	2,134 (51.7)	88.8	88.1	89.5	87.6	87.0	88.3	87.6	86.9	88.3	88.6	87.8	89.5
Very good	1,312 (31.7)	76.9	75.8	78.0	74.5	73.5	75.5	74.4	73.3	75.4	76.4	75.2	77.6
Deteriorating	413 (10.0)	78.3	76.2	80.5	58.1	56.4	59.9	61.0	59.1	63.0	61.1	59.0	63.3
Poor	272 (6.6)	54.7	53.0	56.4	48.3	46.9	49.7	48.0	46.3	49.7	53.9	51.2	56.5

FIG 1. Trajectory groups according to best-fitting model (N = 4131). Solid lines represent the predicted trajectories and dashed lines represent the respective 95% CIs. The table below the figure displays the predicted C30 Summary Score values and respective 95% CIs by trajectory group. C30 Summary Scores were available for 3,816 patients at diagnosis, and then among 3,477 at year-1 follow-up; 3,102 at year-2 follow-up; and 2,241 patients at year-4 follow-up. Higher scores reflect better QOL. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; QOL, quality of life.

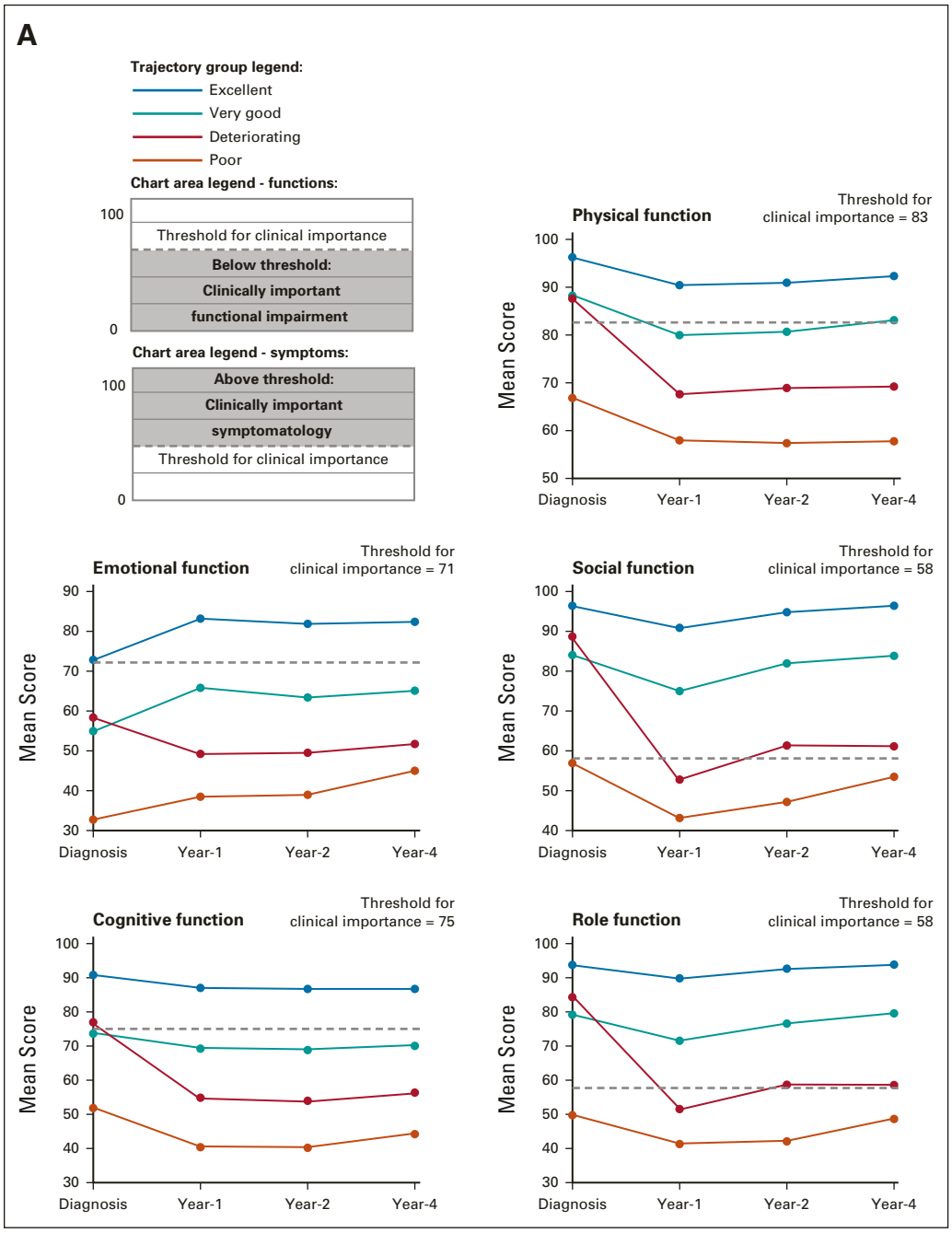


FIG 2. (A) Mean QOL scores by trajectory group and by time point: EORTC QLQ-C30 functions; (B) mean QOL scores by trajectory group and by time point: EORTC QLQ-C30 symptoms. Thresholds for clinical importance are defined by horizontal, dotted gray lines. Higher scores indicate greater functionality and symptomatology. Scores below and above the threshold indicate clinically important functional impairment and symptomatology, respectively (Giesinger JM, et al: *J Clin Epidemiol* 2020). Respective 95% CIs for the means are available in the Data Supplement. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; QOL, quality of life. (continued on following page)

impairment across the four trajectory groups (Figs 2A and 2B, red trajectory lines; Data Supplement).

Trajectory Group Membership

Table 1 displays patient characteristics by trajectory group. Compared with the excellent group, there were consistent associations of membership to the very good, deteriorating, and poor trajectory groups for women with obesity at diagnosis (odds ratio [OR] *v* lean [95% CI]: 1.13 [1.00 to 1.28], 1.51 [1.28 to 1.79], and 1.34 [1.08 to 1.65],

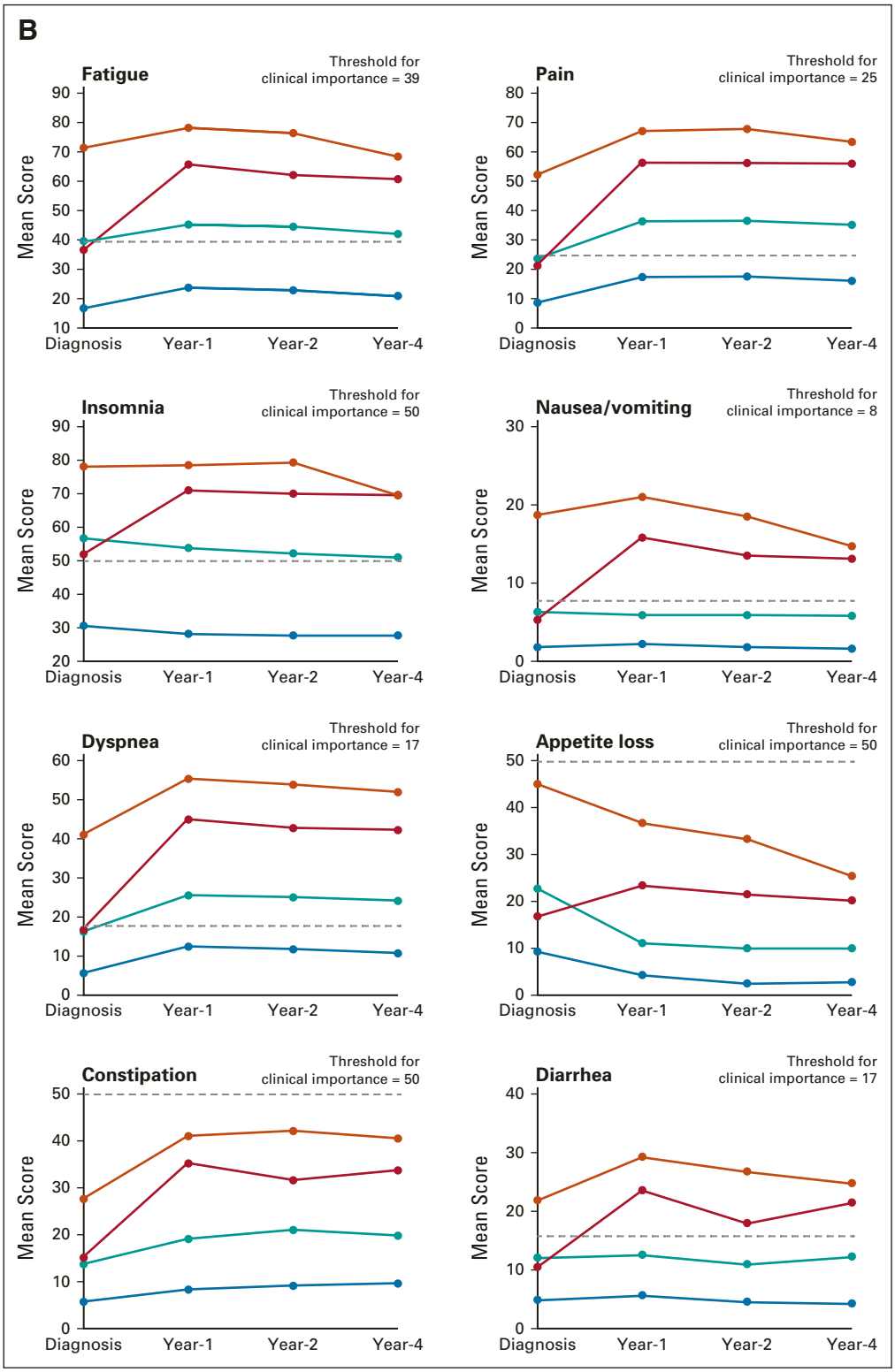


FIG 2. (Continued)

respectively). Current smoker status was also consistently associated with group membership to the deteriorating and poor trajectory groups (ORs *v* never smoker [95% CI], 1.52 [1.27 to 1.82] and 1.82 [1.49 to 2.22], respectively). There were no significant associations between alcohol behavior and group membership. In addition, younger women (adjusted OR for a 1-year decrement [95% CI]: 1.02 [1.01 to 1.02], 1.01 [1.01 to 1.02], and 1.02 [1.01 to 1.03],

respectively), those with comorbidities (adjusted OR *v* no [95% CI], 1.19 [1.08 to 1.31], 1.22 [1.06 to 1.40], and 1.36 [1.15 to 1.60], respectively), and those with lower monthly income (OR *v* women living in wealthier households [95% CI], 1.11 [1.03 to 1.20], 1.21 [1.07 to 1.37], and 1.44 [1.23 to 1.69], respectively) more likely belonged to trajectory groups with very good, deteriorating, and poor QOL patterns compared with excellent patterns, respectively. Receipt of endocrine therapy was significantly associated with increased likelihood of membership to the deteriorating group (OR *v* no [95% CI], 1.14 [1.01 to 1.30]; Table 2).

Health Behaviors and Trajectory Groups

Overall, the proportion of overweight or obese patients was highest among deteriorating and poor groups at diagnosis (56.1% and 54.1%, respectively) and remained highest at year-4 (60.5% and 61.7%, respectively). Some small reductions in weight were observed among patients with obesity in groups at better QOL. There were also differential patterns in PA participation. In the excellent and very good QOL groups, fewer patients at year-4 reported being insufficiently active (not reaching 10 metabolic equivalents of task-hours/week of activity) respective to diagnosis (42.7% at diagnosis and 36.4% at year-4 in the former group and 48.2% at diagnosis and 37.6% at year-4 in the latter group). Conversely, PA was relatively high in the deteriorating group at diagnosis; however, it seemed to decrease through year-4, with a proportion of insufficiently active patients of 42.9% at diagnosis and 46.3% at year-4. The poor group had overall higher rates of insufficient PA participation. In addition, in the deteriorating and poor QOL groups, the prevalence of current smokers at diagnosis was highest (26.3% and 35.4%, respectively), and most of them persisted smoking during chemotherapy (63.7% and 67.1% at year-1, respectively) (Table 3).

Sensitivity Analyses

The results of sensitivity analyses were consistent with main findings. Particularly, number of groups and factors associated with group membership were confirmed in analyses accounting for potential nonrandom dropout and in an expanded analytic cohort (Data Supplement).

DISCUSSION

Using a latent-class analysis, we identified four different trajectories among breast cancer survivors receiving chemotherapy, characterized by excellent (51.7%), very good (31.7%), deteriorating (10.0%), and poor (6.6%) patient-reported QOL patterns. Women clustered in the deteriorating group had significantly worsened QOL following chemotherapy and never recovered to pretreatment values. Excess body weight, reduced PA, and tobacco exposure were frequent among the deteriorating

TABLE 2. Multinomial Logistic Regression of Factors Associated With C30 Summary Score Trajectory Group Membership (*v* reference Excellent, No. = 2,134 [51.7%])

	Very Good (n = 1,312; 31.7%)		Deteriorating (n = 413; 10.0%)		Poor (n = 272; 6.6%)	
Factor	**aOR[a] (95% CI)**	***P***	**aOR[a] (95% CI)**	***P***	**aOR[a] (95% CI)**	***P***
Age, continuous (1-year decrement)	1.02 (1.01 to 1.02)	< .0001	1.01 (1.01 to 1.02)	.043	1.02 (1.01 to 1.03)	< .001
BMI, overweight *v* lean	0.99 (0.89 to 1.11)	.886	0.93 (0.79 to 1.10)	.393	0.99 (0.81 to 1.20)	.902
BMI, obese *v* lean	1.13 (1.00 to 1.28)	.052	1.51 (1.28 to 1.79)	< .0001	1.34 (1.08 to 1.65)	.007
PA, sufficiently *v* insufficiently active	0.91 (0.84 to 0.97)	.008	1.04 (0.93 to 1.17)	.469	0.89 (0.78 to 1.02)	.097
Smoking behavior, current *v* never smoker	1.13 (0.99 to 1.28)	.062	1.52 (1.27 to 1.82)	< .0001	1.82 (1.49 to 2.22)	< .0001
Smoking behavior, former *v* never smoker	1.01 (0.90 to 1.13)	.894	0.79 (0.65 to 0.95)	.011	0.80 (0.65 to 1.00)	.050
Alcohol behavior, daily *v* less than daily	1.02 (0.92 to 1.14)	.683	0.99 (0.84 to 1.17)	.922	1.11 (0.92 to 1.33)	.281
Charlson comorbidity index score, ≥ 1 *v* 0	1.19 (1.08 to 1.31)	< .001	1.22 (1.06 to 1.40)	.005	1.36 (1.15 to 1.60)	< .001
Marital status, partnered *v* not	1.06 (0.96 to 1.16)	.276	1.08 (0.93 to 1.25)	.308	0.96 (0.82 to 1.13)	.659
Income, < 3,000 *v* ≥ 3,000 euro/month	1.11 (1.03 to 1.20)	.010	1.21 (1.07 to 1.37)	.002	1.44 (1.23 to 1.69)	< .0001
BC stage, II *v* I	0.97 (0.88 to 1.07)	.519	1.03 (0.89 to 1.19)	.703	0.95 (0.80 to 1.14)	.582
BC stage, III *v* I	1.00 (0.87 to 1.16)	.988	0.93 (0.75 to 1.16)	.539	1.10 (0.85 to 1.43)	.457
BC surgery, mastectomy *v* partial	1.02 (0.94 to 1.11)	.579	1.01 (0.89 to 1.15)	.860	0.95 (0.81 to 1.10)	.476
Axillary surgery, dissection *v* sentinel node biopsy	1.05 (0.96 to 1.15)	.267	1.14 (0.99 to 1.30)	.060	1.12 (0.95 to 1.33)	.162
Radiation therapy, yes *v* no	0.98 (0.85 to 1.14)	.820	0.93 (0.74 to 1.16)	.495	1.00 (0.75 to 1.33)	.990
Endocrine therapy, yes *v* no	1.05 (0.97 to 1.14)	.195	1.14 (1.01 to 1.30)	.047	0.99 (0.85 to 1.14)	.860
Anti-HER2 therapy, yes *v* no	1.01 (0.93 to 1.10)	.838	0.99 (0.87 to 1.13)	.857	0.98 (0.84 to 1.15)	.823

Abbreviations: aOR, adjusted odds ratio; BC, breast cancer; BMI, body mass index; HER2, human epidermal growth factor receptor 2; PA, physical activity.
[a]Models are adjusted for all the factors in the table.

TABLE 3. Distribution of Health Behaviors by Quality of Life Trajectory Group in the Whole Cohort (N = 4,131)

Health Behavior	Excellent (n = 2,134; 51.7%)	Very Good (n = 1,312; 31.7%)	Deteriorating (n = 413; 10.0%)	Poor (n = 272; 6.6%)
BMI, continuous, mean (SD), kg/m^2				
Diagnosis	25.4 (5.1)	25.8 (5.4)	27.1 (5.9)	26.7 (6.3)
Year-1	25.5 (5.1)	25.9 (5.4)	27.1 (6.0)	26.7 (6.9)
Year-2	25.8 (5.2)	26.2 (5.3)	27.7 (6.0)	27.4 (6.8)
Year-4	25.7 (4.9)	26.1 (5.2)	27.4 (6.0)	27.8 (6.8)
Overweight or obese, %				
Diagnosis	44.7	48.1	56.1	54.1
Year-1	46.6	49.4	57.6	50.0
Year-2	48.0	51.1	60.3	55.6
Year-4	49.6	51.7	60.5	61.7
Mean weight change, kg (95% CI) compared with diagnosis				
Among obese at diagnosis	n = 354 (16.7%)	n = 260 (19.9%)	n = 115 (27.9%)	n = 68 (25.2%)
Year-1	–1.00 (–1.67 to –0.33)	–1.37 (–2.11 to –0.62)	–0.49 (–1.61 to +0.63)	+1.53 (–0.11 to +3.17)
Year-2	–0.07 (–0.89 to +0.75)	–0.76 (–1.69 to +0.17)	+0.70 (–0.55 to +1.96)	+2.17 (+0.29 to +4.05)
Year-4	–0.91 (–1.83 to +0.01)	–2.67 (–4.16 to –1.19)	+0.34 (–1.34 to +2.01)	+0.40 (–2.50 to +3.30)
Lost at least 5% of weight compared with diagnosis, %				
Among obese at diagnosis[a]	n = 354 (16.7%)	n = 260 (19.9%)	n = 115 (27.9%)	n = 68 (25.2%)
Year-1	27.6 (88/319)	25.8 (61/236)	21.1 (23/109)	14.7 (9/61)
Year-2	23.4 (68/290)	25.8 (57/221)	20.2 (21/104)	11.1 (6/54)
Year-4	28.8 (67/233)	32.2 (56/174)	23.5 (19/81)	26.7 (12/45)
Level of PA, continuous, MET-hours/week				
Total activity, median (Q1-Q3)				
Diagnosis	14.0 (0.0-36.0)	10.0 (0.0-36.0)	12.0 (0.0-54.0)	9.5 (0.0-50.0)
Total activity, absolute change, mean (95% CI) compared with diagnosis				
Year-1	–2.73 (–5.84 to +0.38)	–0.07 (–4.10 to +3.95)	–7.58 (–16.19 to 1.03)	–14.41 (–30.37 to +1.54)
Year-2	–1.89 (–5.24 to +1.45)	–1.36 (–5.29 to +2.57)	–12.81 (–21.62 to –4.00)	–12.43 (–28.25 to +3.39)
Year-4	–2.32 (–6.65 to +2.02)	+2.62 (–2.64 to +7.88)	–12.48 (–23.81 to –1.15)	–9.41 (–31.86 to +13.04)
Transport and leisure-time activity, median (Q1-Q3)				
Diagnosis	10.0 (0.0-24.0)	6.7 (0.0-20.0)	4.0 (0.0-18.0)	0.3 (0.0-18.7)
Transport and leisure-time activity, absolute change, mean (95% CI) compared with diagnosis				
Year-1	+1.61 (+0.29 to +2.93)	+4.25 (+2.39 to +6.11)	+1.29 (–2.92 to +5.50)	+2.00 (–3.70 to +7.71)
Year-2	+2.28 (+0.76 to +3.80)	+4.02 (+2.39 to +5.66)	–5.24 (–9.22 to –1.27)	+2.46 (–6.09 to +11.01)
Year-4	+2.00 (+0.13 to +3.87)	+6.07 (+3.76 to +8.39)	–1.72 (–6.70 to +3.26)	+0.66 (–8.98 to +10.30)
Insufficiently active (< 10 MET-hours/week), %				
Diagnosis	42.7	48.2	42.9	50.0
Year-1	35.6	38.8	43.3	46.4

(continued on following page)

TABLE 3. Distribution of Health Behaviors by Quality of Life Trajectory Group in the Whole Cohort (N = 4,131) (continued)

Health Behavior	Excellent (n = 2,134; 51.7%)	Very Good (n = 1,312; 31.7%)	Deteriorating (n = 413; 10.0%)	Poor (n = 272; 6.6%)
Year-2	36.6	39.5	45.0	47.7
Year-4	36.4	37.6	46.3	52.1
Smoke behavior among current smokers at diagnosis, %				
Persistence or increased use compared with previous visit	n = 339 (16.1%)	n = 260 (20.2%)	n = 107 (26.3%)	n = 96 (35.4%)
Year-1	55.4	61.0	63.7	67.1
Year-2	50.2	45.7	50.6	54.3
Year-4	44.9	46.6	47.6	44.9
Alcohol use behavior among daily consumers at diagnosis, %				
Persistence or increased use compared with previous visit	n = 281 (13.6%)	n = 173 (13.6%)	n = 53 (13.2%)	n = 42 (16.0%)
Year-1	88.4	85.3	83.0	82.3
Year-2	86.4	75.0	67.3	70.0
Year-4	85.4	76.0	67.6	68.2

NOTE. Evaluation as to whether weight loss was purposeful cannot be performed. Caution is advised in interpretation of changes over time, especially in smaller groups where mean changes may be driven by extreme values.

Abbreviations: BMI, body mass index; MET, metabolic equivalents of task; PA, physical activity; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

[a]A weight change as low as 5% of baseline can be considered clinically meaningful.

trajectory group. Factors associated with membership to this group also included younger age, comorbidities, lower income, and endocrine therapy.

Although the majority of patients in our cohort had fairly good QOL trajectories, for two specific patient clusters, the long-term QOL dynamics were worryingly worse. The deteriorating QOL group was most affected by primary treatment, experiencing a dramatic drop from diagnosis to year-1, which never recovered. A sharp deterioration was observed for multiple functions in this segment, particularly physical, social, cognitive, and role function, and symptoms including fatigue and pain. These changes can be dramatic from a patient's perspective, qualifying as moderately-to-very-much worse than before treatment,[53] and are considered of medium-to-large magnitude.[54] Almost all mean scores of the deteriorating trajectory group met validated thresholds of clinical importance, red-flagging functional impairment and severe symptoms that should trigger clinician attention and urge dedicated supportive care.[52]

Previous literature tried to describe postchemotherapy changes in QOL, albeit most of it did not comprehensively explore long-term patterns, only captured population averages, or was focused on specific symptoms.[6,7,14,15] Here, we present several elements of novelty, providing a nuanced description of QOL trajectories 4 years after diagnosis, comprehensively assessing overall and specific QOL metrics, and offering insight into the characteristics of latent subpopulations with persistent deterioration.

Our data add to the knowledge about the relationship of several host factors and behaviors with patients' QOL. Women with obesity and current smokers were most likely to cluster into the deteriorating QOL group, where excess weight increased to more than 60% prevalence at year-4 and smoking persistence was frequent during chemotherapy. Surprisingly, women with deteriorating QOL patterns had high PA levels at diagnosis, and the majority adhered to PA recommendations. Nevertheless, this group seemed to have a decline in total PA participation, including reduced work-related PA (perhaps reflecting physical efforts that patients were not able to maintain) and seemed not to substantially increase their leisure-time exercise including sports or recreational PA (compared, for example, to the very good QOL group).

From a biologic standpoint, studies suggested that QOL deterioration may be mediated by the observed unhealthy behaviors. An interplay was described between higher BMI and reduced exercise exposure with alterations in circulating biomarkers, such as inflammation-axis effectors, immunomodulatory cytokines, metabolic-steroid hormones, and growth factors, which can contribute to symptom deterioration and worse treatment-related side effects.[18,55-58] Similar inflammatory alterations, exacerbated by tissue hypoxia and hormone level and circadian rhythm disruptions, were observed in persistent smokers.[23,24,59-61] Adaptation to less physically demanding tasks, as a consequence of decreased PA levels, may also lead to

progressive deconditioning, a process of decline in cardiorespiratory and muscular functional capacity,[62] which previous literature linked to reduced fitness, limited physical performance, and worsening cancer-related symptoms, such as fatigue.[20,22] Finally, reduction in serum estrogen and higher symptom burden associated with endocrine therapy—another of the factors associated with membership to this trajectory—may have deleterious physiologic consequences on multiple systems and interfere with exercise capacity and tolerance.[62,63]

Whether behavioral changes occurring after diagnosis of BC can influence recurrence and cancer-related outcomes, including QOL, is the subject of vivid research. Lifestyle interventions proved safe, feasible, and effective for several outcomes in women with BC.[18,64-68] For example, exercise training during and after completion of chemotherapy led to improvements in physiologic variables and psychosocial status,[69] with beneficial effects on QOL.[19] Behavioral trials of weight loss in overweight and obese BC survivors showed an impact on QOL that was particularly evident on physical function, vitality, and comorbid conditions, but most benefits tended to diminish over time, a finding that is mostly attributed to recidivism and weight regain during postintervention follow-up.[70-72] Ongoing randomized trials will provide additional PROs data and test whether combined interventions of weight loss (ie, with multiple components of improved diet, PA, and personalized behavioral coaching),[73-75] or smoking cessation programs[64,76] are able to reduce treatment-related symptoms, improve QOL, and affect clinical outcomes of BC survivors.

Our findings also highlight contextual, nonbehavioral factors, such as lower income, as strong determinants of membership to trajectory groups with worse QOL. Previous studies suggested that patients from low social classes usually have prolonged post-treatment recovery time and are often at risk of severely impaired physical and psychosocial health.[77] Contributing factors may include lower purchasing power and limited access to supportive care options requiring out-of-pocket expenditures, or job instability and dissatisfaction leading to poor social and role functioning.[78] A higher socioeconomic class may also afford better opportunities and flexibility to modulate behavioral factors, and facilitate the uptake of a healthier lifestyle.[79] Taken together, these data call for a need to proactively promote and prioritize social work interventions in the clinical setting, targeting patient subgroups with indicators of socioeconomic disadvantage that may recover more slowly and remain disabled after chemotherapy. A better understanding of social determinants of health is all the more important in our cohort of BC survivors, where having universal access to health care does not seem to mitigate the impact of social factors as a driver of disparities in health-related outcomes.

Finally, adjuvant endocrine therapy specifically contributed to membership to the deteriorating QOL group. In our previous CANTO analysis,[80] endocrine therapy acted as a major player determining a similar, persistent detrimental impact on QOL. Analogously, the resolution of many systemic therapy–associated symptoms was delayed among patients receiving endocrine therapy in the Mind Body Study.[63] From a clinical perspective, these findings are particularly relevant. Greater treatment-related symptom burden is among the main reasons for nonadherence and discontinuation of endocrine therapy that ultimately can contribute to poorer clinical outcomes.[81,82] In the context of recently consolidated strategies of endocrine therapy escalation,[83-85] particular attention should be given to specific subgroups, such as younger women, who seem to be at higher risk of QOL deterioration and persistent symptoms.[86]

The strengths of this study include its prospective, longitudinal design, and a large and heterogeneous sample. We analyzed a single, higher-order QOL outcome measure that summarizes multiple scales into a multidimensional response profile, thus avoiding multiple comparisons.[35,38] Specific psychometric properties include robustness against inherent PROs limitations, such as dispositional optimism and response shift.[87-89] A major novelty is the use of GBTM, which avoided summarizing QOL data by fitting a simplistic population mean, and allowing to unmask clinically relevant latent groups.

Among common limitations of longitudinal studies such as CANTO is response attrition particularly at later time points, and the results may be driven by midterm changes. In addition, our models fit CANTO data describing a population of women with early-stage BC who were free of disease at the time of QOL assessments. Second, trajectory groups are not necessarily fixed and may change, as GBTM performs a dynamic grouping that is susceptible to additional follow-up.[45] However, GBTM is particularly robust at accommodating missing outcome data and sensitivity analyses trying to address these points confirmed the robustness of our findings. Caution is advised in interpreting some results such as weight changes, because of difficulty to establish intentionality (eg, of weight loss) and small numbers in certain categories. With only a baseline and year-1 assessment, we could not detail QOL evolution during chemotherapy, although we offer a long-term landscape view revealing variability evidenced only after several years postdiagnosis.

This dynamic portrait of postchemotherapy QOL identifies and characterizes patients at risk of steep, clinically meaningful decline. Some factors that were associated with membership to the deteriorating trajectory were nonmodifiable, such as lower income or endocrine therapy. On the contrary, healthy behaviors were consistently and positively associated with better performing trajectory groups. Weight modulation, PA uptake, and tobacco abstinence are modifiable behaviors and potential tools to combat functional health impairment and symptom exacerbation, mitigating the detrimental impact of chemotherapy. However, behavioral interventions supporting

lifestyle changes may be difficult to implement.[90,91] Personalization is paramount in the current scenario where lifestyle-change programs are not standard of care and cancer is not universally a qualifying diagnosis for third-party reimbursement of behavioral interventions.[65,66,76] To optimize resource utilization, research is increasingly focused on healthy lifestyle-promotion interventions among specific target subpopulations, and on optimal ways to deliver patient-specific behavioral support.[64,66,76] This study offers further insight on screening relevant patient-level factors and identifying at-risk patient clusters suitable for tailored interventions for QOL preservation, including early addressal of behavioral concerns and provision of healthy lifestyle-support programs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Dynamics of Long-Term Patient-Reported Quality of Life and Health Behaviors After Adjuvant Breast Cancer Chemotherapy

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