

Original article

Changes in weight, physical and psychosocial patient-reported outcomes among obese women receiving treatment for early-stage breast cancer: A nationwide clinical study



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ABSTRACT

Background: Evidence on how weight loss correlates to health-related quality-of-life (HRQOL) among obese breast cancer (BC) patients is limited. We aimed to evaluate associations between weight changes and HRQOL.

Methods: We included 993 obese women with stage I-II-III BC from CANTO, a multicenter, prospective cohort collecting longitudinal, objectively-assessed anthropometric measures and HRQOL data (NCT01993498). Associations between weight changes ($\pm 5\%$ between diagnosis and post-treatment [shortly after completion of surgery, adjuvant chemo- or radiation-therapy]) and patient-reported HRQOL (EORTC QLQ-C30/B23) were comprehensively evaluated. Changes in HRQOL and odds of severely impaired HRQOL were assessed using multivariable generalized estimating equations and logistic regression, respectively.

Results: 14.1% women gained weight, 67.3% remained stable and 18.6% lost weight. Significant decreases in functional status and exacerbation of symptoms were observed overall post-treatment. Compared to gaining weight or remaining stable, obese women who lost weight experienced less of a decline in HRQOL, reporting better physical function (mean change [95%CI] for gain, stability and loss: -12.9 [$-16.5,-9.3$], -6.9 [$-8.2,-5.5$] and -6.2 [$-8.7,-3.7$]; $P_{\text{interaction[weight-change-by-time]}} = 0.006$), less dyspnea ($+18.9$ [$+12.3,+25.6$], $+9.2$ [$+6.5,+11.9$] and $+3.2$ [$-1.0,+7.3$]; $P_{\text{interaction}} = 0.0003$), and fewer breast symptoms ($+22.1$ [$+16.8,+27.3$], $+18.0$ [$+15.7,+20.3$] and $+13.4$ [$+9.0,+17.2$]; $P_{\text{interaction}} = 0.044$). Weight loss was also significantly associated with reduced odds of severe pain compared with weight gain (OR [95%CI] = 0.51 [$0.31-0.86$], $p = 0.011$) or stability (OR [95%CI] = 0.62 [$0.41-0.95$], $p = 0.029$). No associations between weight loss and worsening of other physical or psychosocial parameters were found.

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Conclusions: This large contemporary study suggests that weight loss among obese BC patients during early survivorship was associated with better patient-reported outcomes, without evidence of worsened functionality or symptomatology in any domain of HRQOL.

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1. Introduction

Obesity is a risk factor for a number of chronic diseases, including diabetes and cardiovascular disease, as well as for early mortality [1]. Several physical, psychological, and social dimensions of health that contribute to the self-perception of quality of life (QOL), referred to as health-related (HR)-QOL, are also negatively impacted by obesity [2].

Obesity has increasingly become recognized as a risk factor also for cancer and as a prognostic factor for individuals diagnosed with early-stage malignancies. Compelling evidence points at the strong link between obesity and breast cancer: excess weight represents a risk factor for postmenopausal breast cancer [3], increases the risk of recurrent and second primary breast cancer [4] and that of overall and breast cancer-specific mortality [5]. Obesity may also interfere with adequate breast cancer treatment delivery [6], exacerbating toxicities and burdening healthcare costs [7]. As the prevalence of obese has risen around the world, the number of obese patients with breast cancer has dramatically increased [8].

Weight changes occurring after diagnosis of early breast cancer are common and post-treatment weight gain is associated with poor HRQOL, body image issues and psychological distress, further aggravating the deterioration of HRQOL that is frequently caused by cancer treatment [9]. Randomized clinical trials reported on some benefits of weight loss on physical function and fitness level of obese individuals [10,11]. Nevertheless, such trials did not address the impact of weight loss on overall HRQOL during or shortly after cancer treatment, and often focused on selected patient groups (e.g. postmenopausal women). In addition, recent large systematic reviews among the general population remarked that studies on obesity, weight loss, and HRQOL have been very heterogeneous in terms of design, study population, and HRQOL assessment [12,13], recommending that research should focus on prospective studies with high retention rates and carefully-chosen HRQOL measures [14].

Because only limited evidence suggests that weight loss in obese breast cancer patients consistently improves HRQOL [14], we aimed to evaluate if weight changes occurring between breast cancer diagnosis and shortly after primary treatment completion are associated with HRQOL. To do so, we used CANTO, a large, contemporary, prospective clinical study of breast cancer survivors that accesses extensive and longitudinal information, including comprehensive serial assessments of patient-reported outcomes (PROs) [15].

2. Methods

CANTO (CANcer TOxicities, ClinicalTrials.gov/NCT01993498) enrolled patients with stage I-II-III breast cancer [16] across 26 French centers. For this sub study, we used data collected at diagnosis (baseline) and during the first visit after primary treatment completion, defined as completion of definitive breast surgery, adjuvant chemotherapy or radiotherapy, as appropriate (adjuvant endocrine therapy and anti-human epidermal growth-factor receptor (HER)-2 therapy were allowed to be ongoing). Study protocol was approved by a central ethical committee for human

subjects. Informed consent was obtained at patient inclusion. Details about the CANTO study procedures were previously published [15].

We accessed information from 5801 women diagnosed from 2012 to 2015. We excluded patients who were not obese at diagnosis (Body Mass Index [BMI]<30.0 kg/m² [N = 4640] or missing [N = 38]), 127 patients with missing post-treatment weight reassessment, and three patients not treated with curative intent (Fig. 1).

Outcome variables. We assessed PROs using the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life-questionnaires QLQ-C30 and QLQ-BR23. The EORTC QLQ-C30 is a 30-item questionnaire that includes a) a global health status subscale, b) five multi-item functional subscales for physical, emotional, social, cognitive, and role functioning, c) three multi-item symptom scales for fatigue, pain, and nausea/vomiting, and d) six single-item symptom scales assessing other cancer-related symptoms including sleep disturbance, dyspnea, appetite loss, constipation, diarrhea, and financial difficulties. The EORTC QLQ-BR23 is the breast cancer-specific companion module to the EORTC QLQ-C30 and consists of 23 items that include a) four functional scales for body image, sexual functioning, sexual enjoyment, and future perspective, and b) four symptom scales for systemic side-effects, breast symptoms, arm symptoms, and upset by hair loss. Questionnaires include two 7-point Likert scale items with response ranging from 'very poor' to 'excellent' for global health, and 4-point Likert scale items with possible responses of 'not at all', 'a little', 'quite a bit, and 'very much' for functioning and symptoms. A standard scoring algorithm was used to convert responses to all items to a 0–100 scale. For global health and functional scales, higher scores reflect a better level of QOL and function, whereas for symptom scales higher scores reflect greater symptom severity compared with lower scores. A validated French version of EORTC QLQ-C30 and QLQ-B23 was used in CANTO [15,17–20] PROs were comprehensively modeled: (1) as continuous; and dichotomizing HRQOL scores by clinical severity, namely (2) HRQOL deterioration from baseline to post-treatment (change ≥ 10 points on global, functional or symptoms scales); (3) prevalence of patients scoring <60 on global/functional or ≥ 40 on symptoms scales, which defined 'poor functions' and 'severe symptoms', respectively; and (4) prevalence of patients transitioning from non-poor function or non-severe symptom at baseline to reporting so post-treatment. All cut-offs were based on previously validated thresholds defining a change as at least "moderate" [21] or considered to define problems of substantial clinical relevance [22] from the patient's perspective.

Independent variables. Weight change between baseline and post-treatment was defined as weight gain $\geq 5\%$, stable weight within $\pm 5\%$, and weight loss $\geq 5\%$. These cut-offs were based on evidence that a weight change as low as 5% of baseline can be clinically meaningful, including being associated with cardiovascular and metabolic disease risk factors and outcomes [23–26].

Covariates. These included clinical variables, socioeconomic status, psychological variables (as per the Hospital Anxiety and Depression Scale [27]), health behaviors (including physical activity as per Global Physical Activity Questionnaire-16 [28]), and type of

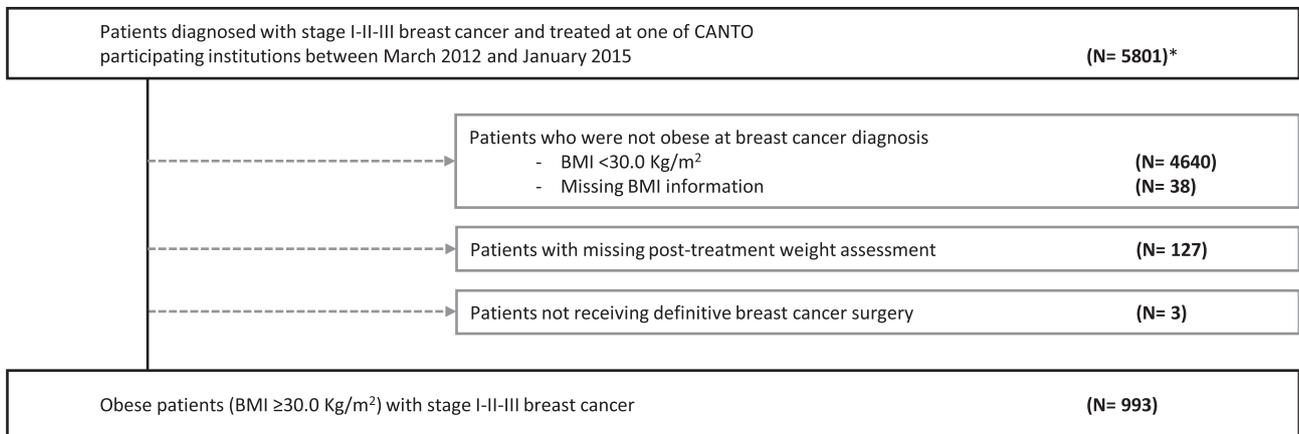


Fig. 1. CONSORT diagram of patient population. *Note: total accrual in CANTO 12012 patients. We accessed information from 5801 women who were enrolled from March 2012 to January 2015.

breast cancer treatment received. Variables were categorized as per Table 1.

2.1. Statistical analysis

Baseline characteristics were tabulated and compared by category of weight change using descriptive statistics.

Associations between outcomes and the independent variable were then examined using different sets of multivariable-adjusted models, which also accounted for baseline HRQOL score (details in respective table footnotes and figure legends).

First, we explored the association between weight change category and HRQOL scores as continuous outcomes. Repeated measurements of HRQOL scores collected from diagnosis to the post-treatment visit were analyzed using the GENMOD procedure and fitting multivariate generalized estimating equations (GEE) with independent correlation structure. We obtained: a) Model-derived least square mean values for HRQOL scores at baseline and post-treatment and b) respective mean least square differences between baseline and post-treatment, according to weight change category (as independent variable). Standard errors and respective 95% Confidence Intervals (CIs) were also calculated. All models accounted for weight change, time, interaction weight-change-by-time, and covariates (ie, age, menopausal status, baseline Body Mass Index, comorbidities, marital status, education, anxiety and depression, smoking status, physical activity, breast and axillary surgery, receipt of chemotherapy, radiation therapy, endocrine therapy, anti-HER2 therapy). To test the hypothesis that the population-averaged HRQOL domain scores differ by weight change category, p-values for the effect of weight change (p_{group}), time (p_{time}) and weight-change-by-time interaction ($p_{\text{interaction}}$) were obtained.

Then, we fit distinct multivariable logistic regression models for each dichotomous outcome to assess odds of HRQOL deterioration and of reporting poor functions or severe symptoms, which returned adjusted odds ratios (aORs) and respective 95% CIs. Logistic regression models were also adjusted for all covariates detailed above.

In sensitivity analyses, we repeated the models by categorizing weight change as $\pm 10\%$ of baseline and as continuous percent-unit change of baseline.

P values < 0.05 were considered significant. All tests were two-sided. Analyses were conducted with SAS v9.4.

3. Results

Our analytic cohort included 993 obese patients. Excluded patients did not differ from those included in the analytic cohort (data not shown). Median time from diagnosis to post-treatment was 10.5 months (interquartile range [IQR] 7.8–12.5). Mean age at diagnosis was 59.1 years (Standard Deviation = 10.5). All patients in this cohort received breast cancer surgery, 91.6% received radiation therapy, and 53.6% received adjuvant chemotherapy. Complete cohort characteristics are displayed in Table 1.

Mean baseline BMI was 34.5 kg/m² (range, 30.0–59.0), mean baseline weight was 89.4 Kg (range, 61.0–153.0). The majority of women, 67.3%, remained stable, 14.1% gained $\geq 5\%$, and 18.6% lost $\geq 5\%$ of baseline weight. Women who lost weight were more likely to be older, postmenopausal, and never smokers (Table 1). Physical activity was associated with weight changes: 59.1%, 63.7% and 73.6% of patients among those who gained, remained stable, or lost weight reported at least same or higher amounts of physical activity post-treatment compared to baseline, respectively (Cochran-Armitage trend test $p = 0.009$; Table 2).

Median completion rate of EORTC-QLQs was 93.6% (IQR 91.0%–94.5%) at baseline and 91.7% (91.1%–92.1%) post-treatment (Supplementary Table 1).

We observed a significant reduction in functional scores and increased symptom scores across the majority of HRQOL domains overall ($p_{\text{time}} < .0001$; Supplementary Table 1) and by weight change (Table 3). Compared to those who gained weight or remained stable, women who lost weight reported less of a decline in HRQOL, including scoring better in physical function (mean change for weight gain, stability and loss [95% Confidence Interval]: -12.9 [$-16.5, -9.3$], -6.9 [$-8.2, -5.5$] and -6.2 [$-8.7, -3.7$], respectively; $p_{\text{interaction}} = 0.006$), dyspnea ($+18.9$ [$+12.3, +25.6$], $+9.2$ [$+6.5, +11.9$] and $+3.2$ [$-1.0, +7.3$], respectively; $p_{\text{interaction}} = 0.0003$), and breast symptoms ($+22.1$ [$+16.8, +27.3$], $+18.0$ [$+15.7, +20.3$] and $+13.4$ [$+9.0, +17.2$], respectively; $p_{\text{interaction}} = 0.044$). Similar patterns suggesting a smaller decrement in HRQOL among those who lost weight were found for other domains (Table 3). Finally, in order to evaluate whether the relationship between weight change and changes in HRQOL differed by receipt of chemotherapy, we introduced weight-change-by-chemotherapy interaction terms in the models, which were not significant ($p_{\text{interaction}} = 0.256$ for physical function, $p_{\text{interaction}} = 0.690$ for dyspnea, and $p_{\text{interaction}} = 0.544$ for breast symptoms).

A substantial proportion of patients (range 15.6–56.5%)

Table 1
Baseline cohort characteristics.

Characteristic, N (%)	Overall	By weight change			p-value [^]
		Gain ≥5%	Stable ±5%	Loss ≥5%	
Baseline BMI, kg/m²	993 (100)	140 (14.1)	668 (67.3)	185 (18.6)	
Mean (SD)	34.5 (4.1)	34.4 (3.8)	34.4 (3.9)	35.2 (4.7)	0.185
Missing	—	—	—	—	
Baseline BMI, WHO categories⁵³					
Obese class I	640 (64.4)	92 (65.7)	439 (65.7)	109 (58.9)	0.2140
Obese class II	248 (25.0)	34 (24.3)	169 (25.3)	45 (24.3)	
Obese class III	105 (10.6)	14 (10.0)	60 (9.0)	31 (16.8)	
Missing	—	—	—	—	
Baseline weight, continuous, kg					
Mean (SD)	89.4 (12.8)	89.0 (12.1)	88.9 (12.7)	91.5 (13.2)	0.099
Missing	—	—	—	—	
Age at diagnosis, years					
Mean (SD)	59.1 (10.5)	54.2 (10.8)	60.1 (10.5)	59.3 (9.2)	<.0001
Missing	—	—	—	—	
Age at diagnosis, years					
< 50	194 (19.5)	44 (31.4)	118 (17.7)	32 (17.3)	<.0001
50–64	471 (47.4)	72 (51.4)	302 (45.2)	97 (52.4)	
≥65	328 (33.1)	24 (17.2)	248 (37.1)	56 (30.3)	
Missing	—	—	—	—	
Marital status					
In a relationship	687 (74.9)	107 (83.6)	463 (74.4)	117 (70.1)	0.325
Not in a relationship*	230 (25.1)	21 (16.4)	159 (25.6)	50 (29.9)	
Missing	76	12	46	18	
Highest education level achieved					
Primary or lower	256 (27.9)	34 (25.6)	180 (29.0)	42 (24.8)	0.176
High school	451 (49.1)	67 (52.3)	308 (49.6)	76 (45.0)	
College graduate or higher	211 (23.0)	27 (21.1)	133 (21.4)	51 (30.2)	
Missing	75	12	47	16	
Employment status					
Professionally active	379 (40.3)	72 (55.4)	245 (38.4)	62 (36.1)	0.019
Professionally inactive	561 (59.7)	58 (44.6)	393 (61.6)	110 (63.9)	
Missing	53	10	30	13	
Monthly total household income					
<1500 Euro	185 (21.0)	27 (22.5)	124 (20.8)	34 (20.7)	0.579
1500–3000 Euro	421 (47.8)	55 (45.8)	294 (49.3)	72 (43.9)	
≥3000 Euro	274 (31.1)	38 (31.7)	178 (29.9)	58 (35.4)	
Missing	113	20	72	21	
Menopausal status					
Premenopausal	249 (25.6)	55 (40.4)	151 (23.1)	43 (23.6)	0.001
Postmenopausal	724 (74.4)	81 (59.6)	504 (76.9)	139 (76.4)	
Missing	20	4	13	3	
Charlson comorbidity index					
0	614 (68.9)	91 (71.6)	410 (68.4)	113 (68.5)	0.594
1+	277 (31.1)	36 (28.4)	189 (31.5)	52 (31.5)	
Missing	102	13	69	20	
Anxiety, score					
Mean (SD)	8.8 (4.2)	8.6 (4.1)	8.9 (4.4)	8.6 (3.9)	0.644
Missing	62	11	40	11	
Anxiety, categorical					
Non-case	387 (41.6)	50 (38.8)	269 (42.8)	68 (39.1)	0.769
Doubtful case	246 (26.4)	41 (31.8)	153 (24.4)	52 (29.9)	
Case	298 (32.0)	38 (29.4)	206 (32.8)	54 (31.0)	
Missing	62	11	40	11	
Depression, score					
Mean (SD)	4.5 (3.7)	4.4 (3.6)	4.4 (3.6)	4.7 (3.9)	0.775
Missing	62	11	40	11	
Depression, categorical					
Non-case	736 (79.0)	97 (75.2)	504 (80.2)	135 (77.6)	0.202
Doubtful case	131 (14.1)	25 (19.4)	82 (13.1)	24 (13.8)	
Case	64 (6.9)	7 (5.4)	42 (6.7)	15 (8.6)	
Missing	62	11	40	11	
Smoking behavior					
Current smoker	106 (10.8)	28 (20.4)	63 (9.6)	15 (8.2)	0.017
Former smoker	200 (20.5)	32 (23.4)	132 (20.1)	36 (19.7)	
Never smoker	671 (68.7)	77 (56.2)	462 (70.3)	132 (72.1)	
Missing	16	3	11	2	
Baseline alcohol consumption					
Daily consumption	859 (89.9)	17 (12.7)	60 (9.3)	19 (10.6)	0.256
Less than daily consumption	96 (10.1)	117 (87.3)	582 (90.6)	160 (89.4)	
Missing	38	6	26	6	
Physical Activity, MET-hours/week					
Median (IQR)	8.0 (0.0–26.7)	12.0 (0.0–48.0)	8.0 (0.0–26.0)	8.0 (0.0–19.0)	0.215
Missing	70	13	45	12	

Table 1 (continued)

Tumor stage					
I	438 (44.1)	56 (40.0)	317 (47.5)	65 (35.1)	0.007
II	431 (43.4)	64 (45.7)	272 (40.8)	95 (51.4)	
III	123 (12.4)	20 (14.3)	78 (11.7)	25 (13.5)	
Missing	1	–	1	–	
Tumor subtype					
HR+/HER-	786 (79.6)	97 (69.3)	557 (83.8)	132 (72.1)	<.0001
HR±/HER2+	127 (12.8)	22 (15.7)	71 (10.7)	34 (18.6)	
HR-/HER2-	75 (7.6)	21 (15.0)	37 (5.6)	17 (9.3)	
Missing	5	–	3	2	
Breast surgery					
Partial surgery	746 (75.1)	107 (76.4)	508 (76.0)	131 (70.8)	0.471
Mastectomy	247 (24.9)	33 (23.6)	160 (24.0)	54 (29.2)	
Missing	–	–	–	–	
Axillary surgery					
Axillary dissection	436 (43.9)	70 (50.0)	289 (42.3)	77 (41.6)	0.386
Sentinel lymph node**	557 (56.1)	70 (50.0)	379 (56.7)	108 (58.4)	
Missing	–	–	–	–	
Adjuvant radiation therapy					
Yes	908 (91.6)	129 (92.1)	615 (92.3)	164 (88.6)	0.354
No	83 (8.4)	11 (7.9)	51 (7.6)	21 (11.3)	
Missing	2	–	2	–	
(Neo) adjuvant chemotherapy					
Yes***	532 (53.6)	84 (60.0)	314 (47.0)	134 (72.4)	<.0001
No	461 (46.4)	56 (40.0)	354 (53.0)	51 (27.5)	
Missing	–	–	–	–	
Adjuvant endocrine therapy					
Yes****	829 (83.5)	105 (75.0)	575 (86.1)	149 (80.5)	0.0008
No	164 (16.5)	35 (25.0)	93 (13.9)	36 (19.5)	
Missing	–	–	–	–	
Adjuvant anti-HER2 therapy					
Yes	97 (9.8)	18 (12.9)	49 (7.3)	30 (16.2)	0.0006
No	896 (90.2)	122 (87.1)	619 (92.7)	155 (83.8)	
Missing	–	–	–	–	

BMI= Body Mass Index; WHO= World Health Organization; SD= Standard Deviation; IQR = interquartile range; HR= Hormone-receptor; HER2 = Human Epidermal Growth Factor receptor 2; MET = Metabolic Equivalent of Task.

^Jonckheere-Terpstra test statistics *Includes separated, divorced, widowed, unmarried **Includes 7 patients who did not receive any axillary lymph node surgical procedure; ***Includes approximately 90% women receiving an anthracycline + taxane chemotherapy combination; ****Patients receiving endocrine therapy were at a median of 3.9 months (IQR 3.0–5.5 months) since treatment initiation at the time of this analysis.

Table 2

Metrics of change in weight and physical activity from baseline to post-treatment.

Characteristic Total	Overall N (%) = 993 (100)	By weight change category		
		Gain ≥5% N (%) = 140 (14.1)	Stable ±5% N (%) = 668 (67.3)	Loss ≥5% N (%) = 185 (18.6)
Post-treatment BMI, kg/m²				
Mean (SD)	34.3 (4.4)	37.3 (4.3)	34.4 (3.9)	31.8 (4.7)
Missing	–	–	–	–
Post-treatment weight, kg				
Mean (SD)	88.9 (13.4)	96.5 (13.3)	89.1 (12.7)	82.4 (12.7)
Missing	–	–	–	–
Change in weight, kg				
Absolute change, mean (95% CI)	–0.5 (–0.9,–0.2)	+7.5 (+6.9,+8.0)	+0.1 (–0.1,+0.3)	–9.0 (–9.7,–8.3)
Percent change, mean (95% CI)	–0.5 (–0.9,–0.1)	+8.4 (+7.8,+9.1)	+0.2 (–0.01,+0.4)	–9.9 (–10.6,–9.2)
Missing	–	–	–	–
Total Physical Activity behavior, N (%)				
Maintained/Increased	559 (65.0)	68 (59.1)	371 (63.7)	120 (73.6)
Reduced	301 (35.0)	47 (40.9)	211 (36.2)	43 (26.4)
Missing	133	25	86	22

BMI= Body Mass Index; SD= Standard Deviation; CI= Confidence Interval; IQR = interquartile range; MET = Metabolic Equivalent of Task.

experienced at least moderate HRQOL-deterioration (Supplementary Fig. 1A). In several domains, including dyspnea and body image, weight loss was associated with a smaller prevalence of patients experiencing such deterioration. Women who lost weight seemed also more likely to report reduced appetite over time (Supplementary Fig. 1B).

Women tended to report poor function and severe symptoms more often post-treatment (Fig. 2A), although this happened less frequently among women who lost weight (Fig. 2B). Particularly,

weight loss was associated with a significant reduction in the odds of reporting poor physical function (aOR [95% CI] = 0.51 [0.27–0.95], $p = 0.033$), poor social function (aOR [95% CI] = 0.45 [0.22–0.93], $p = 0.031$), poor role function (aOR [95% CI] = 0.52 [0.28–0.98], $p = 0.046$), severe pain (aOR [95% CI] = 0.51 [0.31–0.86], $p = 0.011$), and severe dyspnea (aOR [95% CI] = 0.32 [0.17–0.61], $p = 0.0006$) compared to weight gain, and with those of reporting severe pain (aOR [95% CI] = 0.62 [0.41–0.95], $p = 0.029$) and severe dyspnea (aOR [95% CI] = 0.55 [0.31–0.97],

Table 3
Post-treatment health-related quality of life and changes from baseline by category of weight change.

HRQOL domain	Gain $\geq 5\%$ N (%) = 140 (14.1)				Stable $\pm 5\%$ N (%) = 668 (67.3)				Loss $\geq 5\%$ N (%) = 185 (18.6)				P _{group}	P _{interaction}
	Mean ^a	SE	Mean change [§]	95% CI for the change Lower Upper	Mean ^a	SE	Mean change [§]	95% CI for the change Lower Upper	Mean	SE	Mean change [§]	95% CI for the change Lower Upper		
EORTC QLQ-C30 Functional Scales														
Global Health	64.8	2.2	-3.3	-7.3 +0.6	62.2	1.6	-2.5	-8.2 -0.6	66.1	2.1	-0.1	-3.3 +3.2	0.048	0.346
Physical Function	67.9	2.3	-12.9	-16.5 -9.3	72.6	1.6	-6.9	-8.2 -5.5	75.6	2.0	-6.2	-8.7 -3.7	0.043	0.006
Emotional Function	73.3	2.5	+1.9	-2.0 +5.8	73.9	2.0	+4.0	+1.5 +6.3	75.6	2.4	+5.6	+1.7 +9.5	0.876	0.425
Social Function	78.4	3.1	-12.1	-17.5 -6.7	80.7	2.0	-10.8	-13.1 -8.6	84.6	2.4	-9.7	-13.6 -5.8	0.035	0.770
Cognitive Function	71.8	3.5	-6.4	-11.2 -1.5	74.3	2.2	-4.6	-6.8 -2.5	74.7	2.7	-5.4	-9.2 -1.5	0.674	0.799
Role Function	68.3	3.2	-13.4	-19.0 -7.9	71.4	2.1	-9.7	-12.1 -7.2	76.2	2.8	-8.0	-12.9 -3.1	0.058	0.335
EORTC QLQ-C30 Symptom Scales														
Fatigue	46.8	3.4	+16.7	+11.2 +22.3	43.5	2.2	+10.9	+8.6 +13.1	42.6	3.0	+10.3	+5.6 +15.0	0.930	0.138
Pain	36.1	3.4	+17.0	+11.7 +22.3	36.0	2.4	+14.4	+11.9 +16.9	31.2	3.1	+12.4	+7.5 +17.4	0.162	0.466
Insomnia	45.6	4.6	+8.2	+0.7 +15.7	44.7	3.3	+2.3	-0.9 +5.5	41.7	4.2	+1.6	-4.0 +7.3	0.535	0.321
Nausea/Vomit	11.3	2.2	+4.3	+0.7 +7.9	8.4	1.3	+3.2	+1.7 +4.7	9.4	1.8	+1.1	-2.1 +4.4	0.103	0.398
Dyspnea	44.6	3.9	+18.9	+12.3 +25.6	31.9	2.6	+9.2	+6.5 +11.9	24.5	3.1	+3.2	-1.0 +7.3	0.0003	0.0003
Appetite Loss	12.3	3.0	-1.7	-6.8 +3.4	12.7	1.9	-0.6	-2.8 +1.6	16.8	2.5	+2.3	-2.6 +7.2	0.329	0.492
Constipation	17.3	3.4	+8.4	+2.7 +14.1	15.9	2.2	+5.7	+3.4 +8.0	16.6	3.2	+10.3	+5.6 +15.1	0.693	0.199
Diarrhea	15.8	3.4	+5.1	-0.3 +10.6	17.0	2.1	+3.4	+0.9 +5.8	18.6	3.1	+3.9	-0.7 +8.6	0.472	0.854
Financial Difficulties	15.7	3.3	+0.9	-5.4 +7.1	15.3	2.2	+4.2	+2.1 +6.3	16.8	2.8	+8.7	+4.2 +13.2	0.555	0.101
EORTC QLQ-B23 Functional Scales														
Body Image	68.0	3.3	-17.6	-23.4 -11.9	71.0	2.3	-12.9	-15.6 -10.3	74.8	2.8	-11.4	-15.9 -6.8	0.236	0.228
Sexual Function	18.6	3.1	+1.0	-3.6 +5.7	17.4	2.2	-2.0	-3.9 -0.2	18.9	2.8	+0.6	-3.9 +5.1	0.980	0.329
Sexual Enjoyment [^]	52.5	4.8	-6.3	-14.2 +1.6	51.5	4.1	-8.2	-12.1 -4.4	51.7	4.1	-5.3	-15.0 +4.4	0.915	0.805
Future Perspective	56.2	3.8	+3.4	-3.23 +10.1	53.4	2.7	+2.5	-0.5 +5.6	53.5	3.2	+7.1	+1.7 +12.4	0.308	0.345
EORTC QLQ-B23 Symptom Scales														
Side Effects	24.1	2.3	+10.9	+6.9 +14.8	22.3	1.4	+10.3	+8.8 +11.8	21.4	1.9	+10.8	+8.0 +13.6	0.353	0.922
Breast Symptoms	33.1	3.2	+22.1	+16.8 +27.3	28.2	1.7	+18.0	+15.7 +20.3	28.1	2.4	+13.4	+9.0 +17.2	0.215	0.044
Arm Symptoms	34.8	3.8	+20.4	+13.6 +27.2	31.0	2.3	+14.2	+11.6 +16.8	29.5	3.0	+14.4	+9.5 +19.3	0.650	0.243
Upset by Hair Loss	39.2	8.3	-8.4	-31.6 +14.8	42.8	6.3	+16.0	+4.7 +27.3	9.3	3.0	+0.2	-22.6 +23.0	0.313	0.123

HRQOL= Health-related Quality of life; EORTC QLQ = European Organisation for Research and Treatment of Cancer Quality-of-Life questionnaire; SE= Standard Error; CI= Confidence Interval; ^aModel-based least square means for HRQOL scores post-treatment by category of weight change; [§]Model-based differences in least squares means from baseline to post-treatment by category of weight change. Estimates were obtained using generalized estimating equations, adjusted for weight change category (group), time, interaction weight change category by time, age, menopausal status, Body Mass Index, comorbidities, marital status, education, smoking status, physical activity, breast and axillary surgery, receipt of chemotherapy, radiation therapy, endocrine therapy, anti-HER2 therapy, anxiety, and depression. P-values for the effect of weight change category (P_{group}) and of interaction weight change category by time (P_{interaction}) on differences in least squares means are reported.

$p = 0.039$) compared to stable weight (Fig. 2B). Consistent results were found in sensitivity analyses (data not shown).

Among the patients who had not reported severe dyspnea at baseline, 13.1% started to report so post-treatment (Supplementary Fig. 2A). Odds of onset of severe post-treatment dyspnea were elevated among women who gained weight (aOR [95% CI] = 1.84 [1.02–3.33], $p = 0.044$) and reduced among women who lost weight (aOR [95% CI] = 0.39 [0.17–0.86], $p = 0.019$) compared to those whose weight remained stable (Supplementary Fig. 2B).

4. Discussion

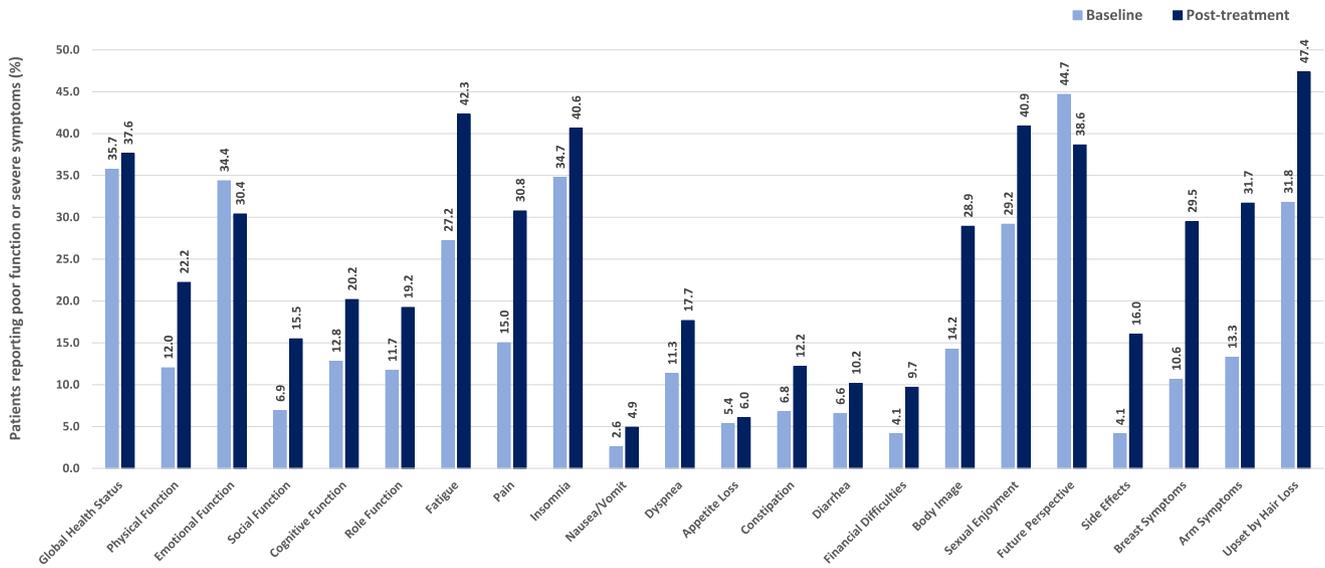
In this large study, we report on the relationship between weight changes and HRQOL in a cohort of obese women with early breast cancer. Overall, patients tended to report reduced HRQOL after breast cancer treatment compared to assessments obtained at diagnosis. Nevertheless, women who gained weight seemed to score the worst in several HRQOL domains, whereas weight loss was associated with more favorable variations in HRQOL. Importantly, there was no association between weight loss and worsened HRQOL after treatment.

Consistently with recent World Health Organization-Europe data, and reflecting the prevalence of obesity in the general French population, obese patients account for almost 20% of the CANTO cohort [29]. Avoiding functional decline and preventing symptom exacerbation among obese women with breast cancer are therefore priorities that concern many providers and patients. In line with past reports, we describe worsening of numerous physical symptoms including fatigue, pain, breast discomfort, and body image issues following breast cancer treatment [30]. Weight gain

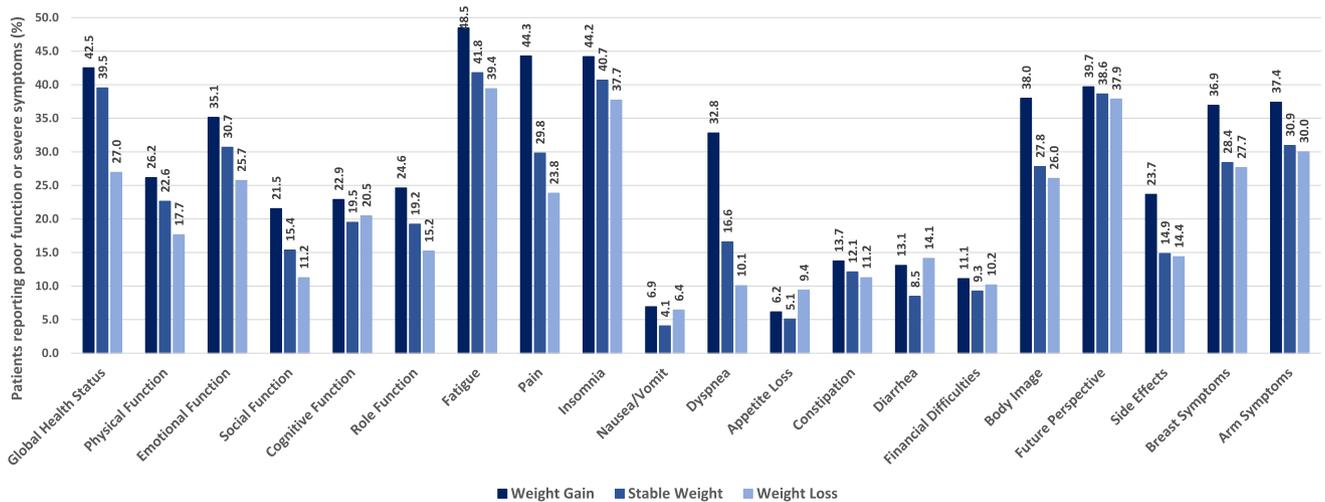
was previously shown to contribute to deterioration of objective physical and cardio-metabolic parameters [31], and here we report that it is also linked with more bothersome, subjective, patient-reported HRQOL-changes. Beyond impaired well-being, post-treatment functional decline leads to loss of independence [32], worse social and cost-related outcomes [33], and possibly impairs cancer-specific outcomes [34], while increased symptom burden is associated with higher rates of non-adherence to adjuvant treatment and worse social rehabilitation in breast cancer survivors [35,36]. Our results inform further studies aimed at testing whether weight control can modulate some of these negative consequences.

In our primary analysis, we reported negative changes in HRQOL after early breast cancer treatment overall, although among women who lost weight we found smaller or negligible changes. According to guidelines provided by Cocks et al. [37], differences in mean HRQOL-changes among women that lost weight were at most trivial-to-small for domains such as physical function and dyspnea (-6.2 and + 3.2 points, respectively), whereas differences in those that gained weight were significantly greater, reaching the range of medium-to-large size (-12.9 and + 18.9 points, respectively). In additional analyses, we adopted particularly conservative cut-offs to categorize PROs (lower than median reference value for functions and higher than median for symptoms) [38], and found that weight loss was also associated with smaller proportions of patients reporting severely impaired HRQOL.

Obesity is now defined as a disease state, and the American Society of Clinical Oncology endorses weight gain prevention and weight loss facilitation for all obese cancer patients [39]. Expert consensus suggests that, for obese women, moderate weight loss of up to one Kg/week can be pursued at any time post breast cancer



A



B

Compared to weight gain												
	Physical Function		Social Function		Role Function		Pain		Dyspnea		Financial Difficulties	
	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Stable	0.76 (0.46-1.24)	0.269	0.75 (0.44-1.28)	0.294	0.83 (0.52-1.32)	0.429	0.83 (0.56-1.24)	0.355	0.58 (0.37-0.93)	0.024	0.62 (0.32-1.18)	0.147
Loss	0.51 (0.27-0.95)	0.033	0.45 (0.22-0.93)	0.031	0.52 (0.28-0.98)	0.046	0.51 (0.31-0.86)	0.011	0.32 (0.17-0.61)	0.0006	0.49 (0.22-1.09)	0.081

Compared to stable weight												
	Physical Function		Social Function		Role Function		Pain		Dyspnea		Financial Difficulties	
	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Gain	1.32 (0.81-2.17)	0.269	1.33 (0.78-2.29)	0.294	1.21 (0.75-1.93)	0.429	1.21 (0.81-1.80)	0.355	1.71 (1.07-2.73)	0.024	1.61 (0.84-3.09)	0.147
Loss	0.67 (0.41-1.10)	0.117	0.60 (0.33-1.09)	0.095	0.63 (0.38-1.06)	0.081	0.62 (0.41-0.95)	0.029	0.55 (0.31-0.97)	0.039	0.80 (0.41-1.58)	0.524

Fig. 2. Prevalence (%) of patients reporting poor function or severe symptoms at baseline and post-treatment in the whole cohort (2A). Prevalence (%) of patients reporting poor function or severe symptoms post-treatment by category of weight change (2B). Poor function is defined by a score <60, severe symptoms by a score ≥ 40 on the respective EORTC QLQ-C30 and QLQ-B23 scales. Prevalence of poor sexual function is not displayed because of scaling of the y-axis (prevalence > 80% in all subgroups). Adjusted odds ratios (aOR) and respective 95% Confidence Intervals (CI) were obtained from multivariable logistic regression models and are reported for selected domains. All models were adjusted for time, age, menopausal status, Body Mass Index, comorbidities, marital status, education, smoking status, physical activity, breast and axillary surgery, receipt of chemotherapy, radiation therapy, endocrine therapy, anti-HER2 therapy, anxiety, and depression.

diagnosis, also during active adjuvant treatment if under appropriate monitoring [40]. However, robust evidence supporting this statement is still lacking. A novel aspect of the present study is that our results did not show that weight loss during or shortly after completion of adjuvant treatment was linked to worsening in HRQOL. Women in our study had a diagnosis of early-stage breast

cancer, and this specific setting is partly responsible for our findings. Prior studies have reported that weight loss during treatment correlates with higher levels of toxicity and poorer outcomes, including cancer-specific survival [41,42], but these studies mostly evaluated disease groups other than breast cancer or patients with more advanced disease. In addition, our study included exclusively

obese women at diagnosis, for whom a beneficial effect of weight loss on health outcomes could be expected, particularly in physical parameters [43].

Lifestyle interventions conducted in overweight or obese breast cancer survivors and that looked at HRQOL include the ENERGY and the LISA studies. ENERGY recruited patients with early-stage breast cancer diagnosed within the previous five years [10], and LISA reported data in women who completed chemotherapy at least four weeks before inclusion [11]. Findings of these studies are consistent with ours, in that a mean weight loss of 6% of baseline in the interventional arm of ENERGY was linked to a more likely preservation of physical function, while participants in the LISA intervention experienced a mean weight loss of 4–5 Kg and reported a greater increase in physical condition, compared to respective control arms [10,11]. Our results expand on this prior work for obese breast cancer patients, highlighting how weight changes occurring during and shortly after adjuvant therapy are related to longer-term HRQOL. There is indeed scarce data from studies that follow up patients with breast cancer from initial diagnosis to post-primary treatment. CANTO offered an unparalleled opportunity to explore the relationship between obesity, weight changes, and HRQOL in early breast cancer survivors in one of the largest contemporary, prospective, longitudinal studies with comprehensive HRQOL assessments. By longitudinally collecting data at several time points after diagnosis, CANTO will also be informative about future questions on the relationship between weight changes and HRQOL occurring later on during the survivorship trajectory [15].

Nevertheless, we acknowledge some limitations. First, it was not possible to assess whether weight loss was purposeful and to establish intentionality of weight changes. However, despite the possibility that some percentages of the observed weight loss were actually unintentional, our comprehensive PRO analyses showed that weight loss was not associated with worsened patient-reported condition in any of the explored outcomes. To improve our understanding of patients' behavioral characteristics, we also assessed other metrics, and found increased physical activity levels among patients who lost weight, an important mediator of successful attempts of weight management [43]. Although it is possible that we could not account for some unmeasured confounders, all our models were also adjusted for change in physical activity behavior, as well as for several important clinical and treatment-related factors. Second, we used a cut-off of 5% to define weight change, based on previously observed clinically meaningful benefits of a weight loss of such magnitude [23]. There has also been substantial variability in values previously used to establish thresholds for HRQOL [44], and universal definitions for EORTC QLQ-C30 and QLQ-BR23 domains are still lacking. However, we provided rationale to support the notion that the chosen cut-offs were clinically relevant. Third, we used self-reported instruments, subject to some recall and reporting biases, but CANTO adopted questionnaires that had already been consistently proven to be reliable and valid instruments for observational studies [45]. Finally, French law does not allow collection of race/ethnicity data, which could have provided relevant information in this context.

5. Conclusions

In conclusion, we have reported several significant associations between weight changes and differential variations in HRQOL of obese women undergoing breast cancer treatment. Our findings were consistent across several domains of general and breast cancer-specific HRQOL, particularly suggesting that weight loss was not associated with worse HRQOL. Weight loss among obese individuals is a complex process, which includes substantial

behavioral changes based primarily on modification of dietary habits and increased energy expenditure. Weight loss interventions are now deemed feasible and also safe in obese breast cancer survivors [11] and randomized trials of weight loss are underway, holding the promise to improve breast cancer outcomes and PROs over the first years following diagnosis [46]. Our study suggests that prevention of weight gain and purposeful weight loss during the early survivorship period should be tested in dedicated studies as strategies to mitigate many downstream *sequelae* of primary breast cancer treatment. Answering this question has important implications, as it would help reduce the burden that secondary effects of breast cancer treatment pose on the care of obese survivors. Finally, from a patient's perspective, the cancer journey contains many “teachable moments” to improve health behaviors, including engaging in weight loss programs. If approached not only as a way to improve one's general well-being and reduce excess weight-related morbidity, but also to pursue functional preservation and symptom management during and after cancer treatment, the goal of weight loss may be more favorably embraced, making attempts more likely successful [31].

Ethical approval

The CANTO study was approved by the national regulatory authorities of France (ID-RCB: 2011-A01095-36) and by the ethics committee CPP IDF VII (11–039). Informed consent for study participation was obtained at patient enrollment.

Data availability

CANTO data is available upon request to a dedicated study Executive Committee (<http://www.unicancer.fr/rd-unicancer/letude-canto>).

Authorship

ADM and IVL: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing - original draft, and writing - review and editing. MEM and ADM: data curation. ADM: formal analysis. SM, AP, FA, and JL: conceptualization, supervision, validation, draft writing. All authors gave substantial contribution to interpretation of data, revised this manuscript for important intellectual content, reviewed and approved its final version.

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Previous presentations

Results of this study were partly presented as a poster display during the European Society for Medical Oncology (ESMO) Congress 2018 (Munich, Germany - October 22, 2018). *Annals of*

Oncology (2018) 29 (suppl_8): viii603-viii640.10.1093/annonc/ndy300.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2020.04.002>.

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