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Longitudinal assessment of the impact of higher body mass index on cancer-related fatigue in patients with breast cancer receiving chemotherapy

Julia E. Inglis¹, Michelle C. Janelins¹, Eva Culakova¹, Karen M. Mustian¹, Po-Ju Lin¹, Ian R. Kleckner¹, Luke J. Peppone¹

¹Department of Surgery, University of Rochester Medical Center (URMC), 265 Crittenden Blvd, CU 420658, Rochester, NY 14642, USA

Abstract

Purpose—To assess the impact of obesity on cancer-related fatigue (CRF) in patients with breast cancer, through a secondary analysis of a large, longitudinal, nationwide study of breast cancer patients beginning chemotherapy.

Methods—All patients ($N = 565$; aged 53 ± 10.6) with breast cancer completed the multidimensional fatigue symptom inventory and the symptom inventory to measure CRF symptoms at baseline, post-chemotherapy, and 6 months post-chemotherapy. Height and weight at baseline were used to categorize subjects based on body mass index (BMI): obese ($> 30.0 \text{ kg/m}^2$; $n = 294$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$; $n = 146$), and normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$; $n = 125$). Multivariate regression models evaluated the relationship of obesity level to CRF over time, controlling for age, menopausal status, race, Karnofsky Performance Status, cancer stage, radiation, and exercise status.

Results—At baseline, the obese had significantly higher CRF symptoms than the normal weight subjects for both the Multidimensional fatigue symptom inventory (MFSI) total (obese = 11.2 vs normal weight = 6.3; $p = 0.03$) and Symptom Inventory (SI) (obese = 3.5 vs normal weight = 2.9; $p = 0.03$). Significantly higher SI fatigue scores persisted at post-chemotherapy for the obese (obese = 5.0 vs normal weight = 4.4; $p = 0.02$). At 6 months post-chemotherapy, the obese patients still had significantly higher SI fatigue scores (obese = 3.5 vs normal weight = 3.0; $p = 0.05$).

Conclusion—Obese patients suffered greater CRF from pre-chemotherapy through 6 months post-chemotherapy. Recommendations for weight loss or weight maintenance may impact CRF levels in obese breast cancer patients before and after chemotherapy.

Julia E. Inglis, Julia_Inglis@URMC.Rochester.edu.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval Furthermore, the authors declare that the protocol herein described complies with the University of Rochester Medical Center and that they obtained institutional review board approval and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Keywords

Cancer-related fatigue; Obesity; Breast cancer; Chemotherapy

Introduction

Over 50% of patients with breast cancer experience gain weight post-chemotherapy [1, 2]. In addition to the impact of treatment, there is already the increased prevalence of obesity in women postmenopause, so that women surviving breast cancer rarely return to their pre-diagnosis weight [1, 3, 4]. Obesity is also more prevalent in patients with breast cancer at the time of diagnosis, being a positive risk factor for disease development postmenopause [3–6].

Cancer-related fatigue (CRF) is experienced by up to 90% of patients with breast cancer and is considered the most persistent and distressing physical impairment post-treatment [7–9]. CRF differs from other types of fatigue in that its development is unrelated to physical overexertion or recent sleeplessness and may persist for years in breast cancer survivors with little improvement [10, 11]. Quality of life (QOL) may also be impacted, so that interpersonal relationships, employment, and work productivity fall into decline [8, 11]. Inflammatory cytokine production and disruption of metabolic processes resulting from cancer and cancer treatment contribute to CRF [12, 13]. Notably, as fat tissue increases in obese patients with breast cancer, there is increased dysfunctional secretion of endocrine factors and inflammatory molecules present. This process is known as the “adipokine hypothesis,” in which adipose cells secrete pro-inflammatory cytokines, much like an endocrine organ [14, 15]. Considering that inflammation promotes CRF and that obese patients have increased chronic low-grade inflammation, it is reasonable to tie obesity in breast cancer patients to CRF and assume CRF may persist longer in this population [16, 17].

In addition, breast cancer survivors often gain weight as a side effect of chemotherapy or hormonal therapy, while simultaneously losing or failing to gain adequate lean tissue, causing the development of the condition termed sarcopenic obesity [18, 19]. This combined condition is characterized by muscle depletion or inadequate levels of lean mass, producing further weakness in the patient with cancer [20]. Sarcopenic obesity in breast cancer survivors could further exacerbate CRF symptoms [21, 22]. Therefore, the impact of CRF in obese patients and survivors may be an area of concern with the increase in obese patients worldwide, especially in patients with breast cancer [23, 24]. The aim of this study was to evaluate the impact of obesity on CRF in breast cancer patients by means of a secondary analysis of a prospective study of breast cancer patients undergoing chemotherapy [25].

Methods

Study population

Data were collected from a prospective, longitudinal nationwide study examining chemotherapy and cognitive function in patients with a diagnosis of invasive breast cancer (stages I to IIIC) [25]. Patients were treated at community oncology clinics affiliated with

the University of Rochester Cancer Control (URCC) National Cancer Institute Community Oncology Research Program (NCORP) Research Base. This secondary analysis evaluated 565 breast cancer patients from pre-chemotherapy until 6 months post-chemotherapy. Outcomes were appraised at three points: within 7 days before chemotherapy (pre-chemotherapy, baseline), within 4 weeks after chemotherapy completion (post-chemotherapy), and 6 months post-chemotherapy (6 months follow-up). Institutional review boards at the University of Rochester and each of the 22 NCORP sites approved the study prior to participant enrollment. A complete description of methods was listed previously [25].

Measures

In this analysis, participants were categorized by obesity status based on body mass index (BMI) at baseline: obese ($\geq 30.0 \text{ kg/m}^2$; $n = 294$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$; $n = 146$), and normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$; $n = 125$). Height and weight were obtained from the clinical record via clinical exam. Karnofsky performance status (KPS), menopausal status, radiation history, and cancer stage were obtained from medical records. Race and exercise status were self-reported where exercise status was based on whether or not participants stated that they exercised weekly on a regular basis over the past 6 months (see Table 1).

Serum albumin levels were measured to evaluate potential malnutrition among groups, although albumin levels may also be influenced by inflammation and stress from cancer and cancer treatment and other chronic conditions [26–28]. Albumin levels were only available at baseline and post-chemotherapy (see Table 2). Symptoms related to CRF were evaluated by the multidimensional fatigue symptom inventory-short form (MFSI-SF) and a CRF question from the Symptom Inventory (SI) questionnaire at all three assessment points. Both the MFSI and SI are reliable and validated in cancer patients and survivors [29, 30].

Statistical analyses

Distribution of baseline characteristics was evaluated, and mean (standard deviation) and n (%) were reported for continuous and categorical measures, respectively. Data were analyzed at baseline, post-chemotherapy, and 6 months post-chemotherapy to evaluate the relationship of baseline obesity level to CRF over time. Missing data were analyzed to ensure they were missing completely at random, across all groups of participants. If data in a variable appeared to not be missing at random, and there were significant missing data in just one group, such as the “obese” group, then that variable would be further evaluated to understand if there was a bias in the model or data collection method. There were 11 participants with missing BMI values at baseline due to having no weight records at baseline, making it impossible to calculate their BMI. Since this is a small proportion of participants (2%) and the paper is about obesity, we excluded these participants from the analysis. More than 50% of the data for participants’ weight were missing for the post-chemo and the 6 months follow-up assessments; therefore, analysis of change in weight over time was not feasible. In general, in the multivariate analysis, if $< 5\%$ of data were missing for any variable, we included the variable in the model. In the case with albumin, however, ~25% of data was missing for all participants at both baseline and post-chemotherapy. However, this is noted later in the paper.

Differences in CRF levels between groups at each time point were assessed using multivariate regression models. Statistical models were adjusted for age, menopausal status, race, KPS, cancer stage, radiation, and exercise status. To confirm the results over time, additional analysis was conducted using linear mixed modeling (LMM) incorporating data from all three time points as repeated measures per participant. A p value < 0.05 was considered significant. All calculations were conducted in SAS 9.4 (SAS Institute, Cary, NC).

Results

This analysis examined CRF symptoms in 565 female patients with breast cancer (mean age 53 ± 10.6 years). For this analysis, 11 participants from the original study were excluded due to extensive missing data related to body weight (BMI) and CRF. At baseline, obese and overweight participants were more likely to be older and postmenopausal (see Table 1). Nearly half did not exercise over the past 6 months across BMI categories. There were no differences in race, KPS, exercise status, cancer stage, radiation history, or other treatment between groups. Serum albumin levels were assessed at baseline and post-chemotherapy, with mean values for all groups at approximately 4.0 g/dL, although there was missing data for albumin for 25% of participants. At post-chemotherapy, there was a decrease in albumin levels for the obese group with a trend toward significance ($p = 0.052$) among the obese (3.9 g/dL) and the other groups (4.0 g/dL) (see Table 2).

Obesity and cancer-related fatigue

All results for CRF are presented as adjusted means. Obesity status throughout the study was categorized based on baseline BMI calculations. Obese patients with cancer consistently presented with the highest scores for CRF symptoms. The obese had greater fatigue at baseline than normal weight participants, with all three groups experiencing an increase in fatigue post-chemotherapy treatment and a decrease in fatigue levels 6 months follow-up post-chemotherapy, where they returned to almost baseline levels (see Figs. 1 and 2). The obese group consistently presented with significantly greater fatigue than the normal weight participants based on the SI fatigue question at baseline and post-chemotherapy and at 6 months post-chemotherapy ($p < 0.05$; see Fig. 1). These results were confirmed in the linear mixed model (LMM) analysis, showing significant changes over time. Generally, a score of 4 or higher on the 11-point SI fatigue question based on fatigue level over the past week indicates CRF in cancer patients and survivors [30]. Mean scores reached 4 and greater at post-chemotherapy in this analysis. Furthermore, throughout the study, the obese patients had higher scores than the normal weight participants based on the MFSI total and MFSI general, although the difference was only significant at the baseline (see Fig. 2). MFSI general may suggest poorer QOL in their experience with cancer and cancer treatment. All other MFSI subscales: physical, emotional, mental and vigor scales were also evaluated among groups without an increased score in the obese (see Table 2).

Discussion

This longitudinal prospective study demonstrated a pattern of greater CRF in the obese patients with breast cancer than normal weight patients over time, from baseline through 6

months follow-up post-chemotherapy. Obesity status was based on baseline BMI where more than half of the participants were obese, which is common in patients with breast cancer. MFSI and SI questionnaires, which were used to assess CRF symptoms, are both validated and reliable in other studies examining CRF in cancer patients and survivors [29, 31, 30]. Based on the SI and MFSI, CRF symptoms increased from baseline to post-chemotherapy and then decreased somewhat again at 6 months follow-up post-chemotherapy. Previous research found that sarcopenic patients have lower levels of serum albumin [32]. In this study, serum albumin levels were normal across all groups, although decreased slightly in the obese group post-chemotherapy. Few other studies have evaluated the relationship of obesity with CRF levels in breast cancer patients longitudinally.

Obese patients experience chronic low-grade inflammation which may further contribute to the disease. The “adipokine hypothesis” asserts that white adipose cells may function as an endocrine organ, secreting hormones that in an auto and paracrine fashion which further contributes to chronic disease [15]. Expanding fat stores in the obese also can lead to dysfunctional secretion of endocrine factors and inflammatory molecules that potentially impact obese breast cancer patients, both preand post-treatment [15, 33]. Furthermore, some studies even link the type of gut microbiota in the obese patient to increased pro-inflammatory cytokine production and secretion [34]. Pro-inflammatory cytokines including interleukin (IL)-1, IL-6, and TNF- α are found in the cancer tumor microenvironment and are also believed to play a mechanistic role in CRF development in breast cancer patients [35]. What the role of obesity and chronic low-grade inflammation plays in CRF development in this population is yet to be elucidated, but findings from this analysis suggest that the obese patient suffers a greater burden of fatigue. Future research is needed to identify which inflammatory molecules are most likely to increase CRF in obese breast cancer patients.

This study supports previous research on CRF in patients with breast cancer. In a study assessing CRF in 337 breast cancer survivors 6 to 42 months post-treatment, those with CRF had higher BMIs and were more likely to be obese at baseline [36]. Other research in breast cancer survivors has also correlated higher BMI with CRF [37–39]. However, the study by Taylor et al. also recognized that greater CRF levels were partly explained by lower activity levels in the obese group [39].

Previous studies have also demonstrated that many times, symptoms present at pre-chemotherapy in cancer patients often become worse post-treatment [40]. In this study, there was increased fatigue with chemotherapy treatment, with subsequent improvement in CRF in all groups 6 months post-treatment, with a persistent difference between obese and non-obese patients. Obesity may play a role in worsening CRF over the course of treatment as well as following chemotherapy, suggesting that weight loss therapy might be warranted in this population pre-chemotherapy [41]. Furthermore, the obese and overweight patients were more likely to be post-menopausal. Weight loss is more difficult postmenopause, due to decreased metabolic rate and lean mass and hormonal changes that lead to increased body fat [42, 43]. Previous studies suggest that this population requires a combined treatment approach that includes increased physical activity, dietary changes, and other behavioral modifications for weight loss interventions to be effective [41, 44, 45]. Currently, most

research on treatment for CRF in breast cancer patients focuses on the impact of exercise or physical activity [46–48]. Further research is needed on the impact of dietary changes, diet combined with exercise interventions, and weight loss on CRF in breast cancer patients and survivors.

Strengths of this study include a large, homogenous, nationwide sample size of patients with breast cancer.

Limitations involve the preliminary nature of this analysis. To evaluate the impact of obesity on fatigue in cancer patients in the future, it would be prudent to also measure levels of pro-inflammatory cytokines in relation to obesity and CRF. This study did not control for chemotherapy dose, sleep quality, or for sociological data such as income level.

Conclusion

In this study, obese patients with breast cancer presented with higher levels of CRF than normal weight patients pre-chemotherapy, over the course of chemotherapy and 6 months post-chemotherapy. Obesity levels at pre-chemotherapy may impact CRF throughout treatment, as well as the severity and duration of CRF post-chemotherapy in patients with breast cancer. Most interventions in breast cancer survivors to reduce CRF focus on exercise and physical activity. Postmenopausal women with breast cancer struggle more with weight loss and obesity. More research is needed on weight loss interventions as well as dietary changes, possibly combined with exercise, to address CRF in obese patients with breast cancer.

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Abbreviations

CRF	Cancer-related fatigue
BMI	Body mass index
QOL	Quality of life
SI	Symptom inventory
MFSI-SF	Multidimensional fatigue symptom inventory-short form
KPS	Karnofsky Performance Status

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Fig. 1.

SI Fatigue scores baseline, post-chemotherapy, and 6 months follow-up post-chemotherapy based on baseline obesity categorization. **p* value obese vs. normal weight participants. SI fatigue, Symptom Inventory fatigue. Means adjusted for age, menopausal status, race, Karnofsky Performance Status, cancer stage, radiation, and exercise status

Fig. 2.
LMM analysis: overall MFSI total and MFSI general scores among groups
Means adjusted for age, menopausal status, race, KPS, cancer stage, radiation and exercise status.
 P -value depicts significant changes between time points for all three groups.

Table 1

Baseline descriptive characteristics of participants (*N* = 565)

Characteristic	Normal (<i>n</i> = 125)	Overweight (<i>n</i> = 146)	Obese (<i>n</i> = 294)	<i>p</i> value
Body mass index, (mean, SD)	22.5 ± 1.7	27.5 ± 1.4	36.8 ± 5.8	<0.001 [*]
Age	51.8 ± 11.0	53.8 ± 11.0	54.2 ± 10.2	0.049 ^{**}
Race (<i>n</i> , %)				0.075
Caucasian	115 (92.0%)	134 (91.8%)	253 (86.0%)	
Other	10 (8.0%)	12 (8.2%)	41 (14.0%)	
Exercise (yes)	68 (54.4%)	79 (54.1%)	152 (51.7%)	0.892
KPS (mean, SD)	96.1 ± 7.5	97.2 ± 6.3	96.6 ± 5.7	0.344
Menopausal status				0.014 [*]
Premenopausal	62 (49.6%)	48 (32.9%)	110 (37.4%)	
Postmenopausal	63 (50.4%)	98 (67.1%)	184 (62.6%)	
Cancer stage				0.682
Stage 1	30 (24.0%)	42 (28.8%)	81 (27.6%)	
Stage 2	62 (49.6%)	70 (47.9%)	142 (48.3%)	
Stage 3	22 (17.6%)	29 (19.9%)	56 (19.0%)	
Unknown	11 (8.8%)	5 (3.4%)	15 (5.1%)	
Radiation (yes)	68 (54.4%)	91 (62.3%)	168 (57.1%)	0.394
Specific agents received [§]				
Cyclophosphamide	97 (77.6%)	107 (73.3%)	220 (74.8%)	
Docetaxel	61 (48.8%)	76 (52.1%)	158 (53.7%)	
Doxorubicin	59 (47.2%)	59 (40.4%)	117 (39.8%)	
Paclitaxel	60 (48.0%)	54 (37.0%)	113 (38.4%)	
Carboplatin	25 (20%)	28 (19.2%)	54 (18.4%)	
Epirubicin	2 (1.6%)	3 (2.1%)	9 (3.1%)	
Fluorouracil	2 (1.6%)	1 (0.7%)	4 (1.4%)	
Methotrexate	0	1 (0.7%)	1 (0.3%)	

^{*} Significant difference in mean values among groups

^{**} Significant difference between normal weight and obese groups only

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[§]Chemotherapy received

p value was based on ANOVA for continuous variables and Chi-square for all categorical variables

Table 2

Changes in serum albumin levels, SI fatigue, MFSI total, and MFSI subscales among groups over the course of treatment, adjusted mean, and standard error

	Baseline			Post-chemotherapy			6 months post-chemotherapy			P value		
	Normal	Overweight	Obese	p value	Normal	Overweight	Obese	p value	Normal		Overweight	Obese
Albumin	4.1 ± 0.1	4.2 ± 0.1	4.1 ± 0.1	.494	4.0 ± 0.1	4.0 ± 0.1	3.9 ± .05	.052	n/a	n/a	n/a	
SI fatigue	2.9 ± 0.2	3.2 ± 0.2	3.5 ± 0.2	.028*	4.4 ± 0.2	4.9 ± 0.2	5.0 ± 0.2	.018*	3.0 ± 0.2	3.4 ± 0.2	3.5 ± 0.2	.046*
MFSI total	6.3 ± 1.9	11.9 ± 1.7	11.2 ± 1.2	.028*	12.1 ± 2.1	14.9 ± 1.9	15.1 ± 1.4	.213	6.7 ± 2.0	8.6 ± 1.9	9.2 ± 1.4	.294
MFSI general	7.0 ± 0.6	8.5 ± 0.5	8.7 ± 0.4	.016*	10.2 ± 0.7	10.7 ± 0.6	10.9 ± 0.5	.372	8.0 ± 0.6	8.4 ± 0.6	8.8 ± 0.4	.280
MFSI physical	3.5 ± 0.4	4.8 ± 0.4	4.3 ± 0.3	.105	6.1 ± 0.5	6.0 ± 0.5	6.6 ± 0.4	.434	4.6 ± 0.5	4.6 ± 0.5	5.1 ± 0.3	.375
MFSI emotional	5.3 ± 0.5	6.0 ± 0.4	5.7 ± 0.3	.408	3.7 ± 0.4	5.1 ± 0.4	4.6 ± 0.3	.088	3.6 ± 0.5	4.6 ± 0.4	4.2 ± 0.3	.250
MFSI mental	4.2 ± 0.4	5.4 ± 0.4	5.2 ± 0.3	.039*	5.8 ± 0.5	6.3 ± 0.5	6.1 ± 0.3	.666	5.7 ± 0.5	5.8 ± 0.5	5.8 ± 0.3	.747
MFSI vigor	13.6 ± 0.4	12.8 ± 0.4	12.8 ± 0.3	.132	13.8 ± 0.5	13.2 ± 0.4	13.1 ± 0.3	.224	15.2 ± 0.4	14.9 ± 0.4	14.8 ± 0.3	.497

* P-value obese vs. normal weight participants

SI fatigue, Symptom Inventory fatigue; MFSI, multidimensional fatigue symptom inventory