

Association between Nutritional Status and Health-Related Quality of Life (HRQoL) in Women with Breast Cancer undergoing Chemotherapy: A Prospective Study

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Abstract

Purpose This study aimed to evaluate the association between chemotherapy (CT) time, nutritional status and the effect of the interaction between these variables on the symptoms and domains of Health-Related Quality of Life (HRQoL). Despite the adverse effects CT, it's common the gain weight and unfavorable changes in the body composition of women during and after the treatment. And an inadequate nutritional status can negatively impact the HRQoL and can influence the prognosis of breast cancer (BC).

Methods This study was carried out with 55 women with BC over three periods of CT, T0, before the first cycle; T1, intermediate period; and T2, after the end of CT. HRQoL was assessed using the 30-Item Quality of Life Questionnaire (QLQ-C30) and its BC module, the Quality of Life Questionnaire Breast Cancer – 23 (QLQ-Br23).

Results Overweight, waist circumference (WC) indicative of increased risk and substantially increased risk of metabolic complications, waist-hip ratio (WHR) indicative of risk of developing chronic diseases, waist-to-height ratio (WHtR) indicative of excess abdominal fat and longer CT times (T1 and T2), each separately, as well as the interaction of these anthropometric variables with CT time, were associated with worse symptom and HRQoL domains scores.

Conclusion The course of treatment and a worse nutritional status, have negative effects on HRQoL, and it is relevant to encourage women with BC undergoing CT to adopt a healthy diet and to practice physical activity in order to maintain an adequate nutritional status, that could contribute to a better HRQoL.

1. Introduction

Breast cancer (BC) is the leading cause of cancer death in women [1] Among the treatment modalities for cancer is chemotherapy (CT) [2]. Recent data from our research group identified that CT negatively interferes with diet and perceptions related to food intake, as well as with the nutritional status and Health-Related Quality of Life (HRQoL) of women with BC [3–6]. HRQoL includes aspects directly related to illnesses, health interventions and the impact of symptoms, disabilities or limitations on functioning and perception of well-being [7].

Despite the adverse effects of CT and dietary inadequacy, between 50 and 96% of women gain weight during the treatment, with a progressive increase in the months and years after diagnosis [8]. In addition, there may be a significant increase in the waist-hip ratio (WHR), a predictor of increased risk for metabolic syndrome [9]. Furthermore, there is the possibility of unfavorable changes in the body composition of these women throughout CT, with sarcopenia (loss of muscle mass), accompanied by increases of adipose tissue, representing a significant risk for the development of comorbidities and worse survival in the long term [8].

It is noteworthy that the body changes presented during CT are not easily reversed after the end of the treatment. On the contrary, many continue to gain weight [10] which is unfavorable, since excess weight, whether gained before or after cancer diagnosis, is a factor that negatively impacts quality of life, prognosis and survival of women with BC [11].

When compared to the population without BC, these women have worse HRQoL, with worse scores for global health status, functional and social capacity, in addition to more symptoms of fatigue and insomnia [12].

Studies indicate that quality of life during CT can be a predictor of the disease's prognosis [13, 14]. Better physical capacity, emotional condition, global health status and lower incidence of nausea and vomiting are predictive factors for survival in women with BC [13]. Additionally, Lee et al. (2010) found that physical well-being and appetite were able to predict overall survival after adjustments, while worse physical well-being was associated with less objective tumor

response, greater risk of weight loss and to non-hematological adverse effects in women with advanced metastatic BC. Evidence points, therefore, that quality of life may be related to the response to CT and the patient's survival [14].

Considering that CT can negatively impact nutritional status and HRQoL [15], the present prospective study aimed to assess the association between CT time, nutritional status and the effect of the interaction of these variables in the HRQoL domains. We hypothesize that women have a worse HRQoL when they have a worse nutritional status at a more advanced stage of treatment.

2. Methods

2.1. Study Design and Ethical Aspects

This is a prospective study conducted between August of 2014 and October of 2015, developed with women with BC undergoing CT at the Clinical Hospital of the Federal University of Uberlandia (HC/UFU). The follow-up time varied according to the CT regimen, which ranged between 4 and 6 months. The evaluations were performed at three moments during CT – T0, before the first CT cycle; T1, CT intermediate period; and T2, after the end of CT. It is emphasized that some data were collected 21 days after each study time. This study was approved by the Ethics Committee on Research with Human Beings (no. 721,977/14, adhering no. 1,111,998/15) and complies with the principles and ethical standards of the Declaration of Helsinki and CNS Resolution 466/12.

2.2. Sample Size and Sample Eligibility

The sample size was statistically determined using the G*Power software, version 3.1 [16]. A total of 43 women were required, considering Anova F-Test of repeated measurements with intermediate effect size of 0.25, alpha level of 0.05, test power of 95%, being a group of individuals and three measurements. Considering a 20% adjustment for possible losses, a minimum of 52 women would be necessary at the beginning of the study (T0) [4]. The inclusion criteria were women aged 18 years or older, diagnosed with primary BC and who were in the first CT cycle at T0. Women with a primary non-breast tumor site, under antineoplastic treatment that did not include CT, with change in treatment due to toxicity or recurrence of the disease, or who were ongoing CT were excluded.

2.2. Data Collection

Socioeconomic, therapeutic and clinical data were extracted from questionnaires completed from interviews and consultation of medical records to characterize the sample. The anthropometric parameters current weight and height were evaluated, following a protocol established by the WHO [17] and using a calibrated mechanical scale with a sensitivity of 100 g and a vertical stameter with an accuracy of 1 mm (model P-150C; Leader Scales, São Paulo, Brazil). The data obtained were used to calculate body mass index (BMI) in Kg/m^2 . In addition, waist circumference (WC) and hip circumference (HC) were collected using flexible and inelastic tape with 1 mm precision to establish waist-hip ratio (WHR) and waist-height ratio (WHtR), using a Lohman, Roche and Martorell protocol [18]. As overweight is known to have a negative influence on quality of life [19], we chose to dichotomize the variable "overweight", in order to enable more robust and easier to interpret analyses. The categorization of BMI into overweight or not took into account the classification by the WHO [20] for adults and Lipschitz [21] for the elderly women. Thus, the variable "non-overweight", including those classified as underweight and eutrophic ($\text{BMI} \leq 24.9 \text{ kg}/\text{m}^2$ or $\text{BMI} \leq 27 \text{ kg}/\text{m}^2$, cut-off points respectively for adults and the elderly); and the variable "overweight", including those overweight and obese ($\text{BMI} \geq 25 \text{ kg}/\text{m}^2$ or $> 27 \text{ kg}/\text{m}^2$, respectively for adults and the elderly) were created. WC was categorized as "below the risk level for metabolic complications" ($\text{WC} < 80\text{cm}$); "high risk for metabolic complications" ($\text{WC} \geq 80\text{cm}$); and "very high risk for metabolic complications" ($\text{WC} \geq 88\text{cm}$) which is according to the classification by the WHO [20]. For WHR and WHtR, cutoff points > 0.85 [20] and ≥ 0.5 [22] were adopted as indicative of risk for developing chronic diseases and indicative of excess abdominal fat, respectively. To evaluate HRQoL, the instruments developed by the European

Organization for Research and Treatment of Cancer (EORTC), the generic 30-Item Quality of Life Questionnaire (QLQ-C30) and its module for BC, the Quality of Life Questionnaire Breast Cancer – 23 (QLQ-Br23), both in the Portuguese version for Brazil [23], by permission of the EORTC for use in scientific research, were used. The application of these questionnaires occurred 21 days after each time of evaluation (T0 + 21 days, T1 + 21 days and T2 + 21 days), always before CT. We chose to investigate only the domains and symptoms that could be more related to anthropometric variables, having been evaluated: Global Health, Global Function, Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning, Symptoms, Fatigue, Pain, Dyspnea, Insomnia, Body Image, Sexual Function, Sexual Satisfaction.

2.1 Statistical analysis

The IBM SPSS Statistics version 21.0 software was used to perform statistical analyses. Descriptive statistics were performed to determine the mean, standard deviation, median and interquartile interval. This study aimed to verify the effect of anthropometric variables, CT time and the interaction between these variables on HRQoL scores and HRQoL symptoms. For this, General Mixed Models (GMM) were used. For those domains and symptoms that did not have the effect of the anthropometric variable and, or interaction, were tested only for the influence of CT time, considering that the treatment alone is enough to impact HRQoL. All analyses were adjusted for age, schooling, income and menopausal status. The estimated marginal means and 95% confidence intervals (CI) were compared to the pairs applying Sidak for multiple tests.

3. Results

This study included 55 women with a mean age of 51.5 ± 10.1 years. The clinical, therapeutic and sociodemographic characteristics, as well as the nutritional status are shown in Table 1. Anthropometric measurements have already been detailed in previous studies by our group [24, 4]. The mean weight of these women at the beginning and at the end of treatment was 70.9 ± 16.4 kg and 71.8 ± 16.8 kg, respectively, presenting a statistically significant change ($p = 0.008$). During treatment, these women also had an increase in BMI ($p = 0.009$) and WC ($p = 0.030$), emphasizing that they had already started treatment with excess weight (T0, 28.4 ± 6.4 kg / m²) and WC, indicative of increased risk for metabolic complications (T0, 90.8 ± 15.7 cm). The WHtR and WHR did not have statistically significant changes during the treatment, however, since the beginning of CT these measures were above the recommended (WHtR > 0.5 and WHR > 0.85), indicating excess abdominal fat and risk for the development of chronic diseases, respectively.

Table 1
Clinical, hormonal, therapeutic and sociodemographic characteristics of women with breast cancer.

Characteristics n (%)	Total (n = 55)	BMI (T0)	
		Non-overweight (n = 24)	Overweight (n = 31)
Age (years) mean (min-max ± SD)	51.5 (29–66 ± 10.1)	52.5 (29–66 ± 11.6)	50.7 (38–66 ± 8.9)
Marital Status			
With partner	33 (60)	14 (58.3)	19 (61.3)
Without partner	22 (40)	10 (41.7)	12 (38.7)
Family Income			
≤ 2 minimum wage	29 (52.7)	10 (41.7)	19 (61.3)
> 2 minimum wage	26 (47.3)	14 (58.3)	12 (38.7)
Years of Schooling			
≤ 9 years	24 (43.6)	8 (33.3)	16 (51.6)
9 to 12 years	18 (32.7)	8 (33.3)	10 (32.3)
> 12 years	12 (21.8)	8 (33.3)	4 (12.9)
NR	1 (1.8)	0	1 (3.2)
Menopause			
No	21 (38.2)	7 (29.2)	14 (45.2)
Yes	34 (61.8)	17 (70.8)	17 (54.8)
Tumor Subtype			
Ductal carcinoma	53 (96.4)	24 (100)	29 (93.5)
Lobular carcinoma	2 (3.6)	0	2 (6.5)
Clinical Stage			
0	1 (1.8)	1 (4.2)	0
IA	10 (18.1)	7 (29.2)	3 (9.7)
IIA	12 (21.8)	1 (4.2)	11 (35.5)
IIB	14 (25.4)	5 (20.8)	9 (29)
IIIA	6 (10.9)	4 (16.7)	2 (6.5)
IIIB	8 (14.5)	3 (12.5)	5 (16.1)

BMI, Body Mass Index; T0, before the first chemotherapy infusion cycle; SD, standard deviation; G1, well-differentiated tumor (low grade); G2, moderately differentiated tumor (intermediate grade); G3, poorly differentiated tumor (high degree); ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor type 2 receptor; -, negative; + positive; CK, cytokeratin; EGFR, human epidermal growth factor receptor; Ki 67, Ki 67 antigen; NR, not registered; AC, adriamycin + cyclophosphamide; FAC, 5-fluoracil, adriamycin and cyclophosphamide; CMF, cyclophosphamide, methotrexate and 5-fluorouracil.

Characteristics n (%)	Total (n = 55)	BMI (T0)	
		Non-overweight (n = 24)	Overweight (n = 31)
IV	1 (1.8)	1 (4.2)	0
NR	3 (5.4)	2 (8.3)	1 (3.2)
Histological Grade			
G1	7 (12.7)	4 (16.7)	3 (9.7)
G2	32 (58.2)	14 (58.3)	18 (58.1)
G3	12 (21.8)	3 (12.5)	9 (29)
NR	4 (7.3)	3 (12.5)	1 (3.2)
Molecular Subtypes			
ER-, PR-, HER2- and CK5/6 + and/or EGFR+	11 (20)	3 (12.5)	8 (25.8)
ER-, PR- and HER2+	7 (12.7)	4 (16.7)	3 (9.7)
ER + and/or PR+, HER2- and Ki-67 < 14%	14 (25.4)	7 (29.2)	7 (22.6)
ER + and/or PR+, HER2- and Ki-67 ≥ 14%	18 (32.7)	8 (33.3)	10 (32.3)
ER + and/or PR+, HER2+	5 (9.1)	2 (8.3)	3 (9.7)
Chemotherapy Protocol			
AC◇ Docetaxel	33 (60)	14 (58.3)	19 (61.3)
AC◇ Paclitaxel	8 (14.5)	3 (12.5)	5 (16.1)
FAC	9 (16.4)	4 (16.7)	5 (16.1)
CMF	5 (9.1)	3 (12.5)	2 (6.5)
BMI, Body Mass Index; T0, before the first chemotherapy infusion cycle; SD, standard deviation; G1, well-differentiated tumor (low grade); G2, moderately differentiated tumor (intermediate grade); G3, poorly differentiated tumor (high degree); ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor type 2 receptor; -, negative; + positive; CK, cytokeratin; EGFR, human epidermal growth factor receptor; Ki 67, Ki 67 antigen; NR, not registered; AC, adriamycin + cyclophosphamide; FAC, 5-fluoracil, adriamycin and cyclophosphamide; CMF, cyclophosphamide, methotrexate and 5-fluorouracil.			

In relation to HRQoL, we observed that women who were overweight (BMI ≥ 25 kg/m² or > 27 kg/m², respectively for adults and elderly), had a lower score on Physical Functioning (p = 0.023) and a higher score on fatigue (p = 0.017). At the end of CT (T2), lower scores for the Global Function (p < 0.001) and Physical Functioning (p < 0.001) were identified, and a higher Fatigue score (p = 0.003), in relation to the beginning of treatment (T0). In addition, statistically significant effects of the interaction between BMI and CT time on the Global Function (p = 0.040) and Physical Functioning (p = 0.011) were identified at T2; on insomnia (p = 0.003), at T1; and dyspnea (p = 0.035), however, for this symptom, it was not identified by the post-hoc at which time of treatment the significance occurred (Table 2).

Table 2

Model Effects Tests of the Body Mass Index (BMI) and Chemotherapy (CT) Time in the domains of Health-Related Quality of Life (HRQoL).

Dependent Variables		Independent Variables				Model Effects Test				
		CT Time, BMI and BMI with CT Time								
CT Time		BMI				Effects	Df	p		
		Non-overweight (n = 73)		Overweight (n = 92)						
Mean	SE	Mean	SE	Mean	SE					
Global Function				70.08	4.84	65.51	5.65			
T0	74.84 ^a	5.23	77.70	5.70	71.98	6.22	BMI	1	0.28	
T1	67.75 ^{a,b}	5.23	64.93	5.78	70.58	6.27	CT Time	2	< 0.001	
T2	60.79 ^b	5.24	67.61 ^a	5.60	53.98 ^b	6.31	BMI * CT Time	2	0.04	
Physical Functioning				76.18	4.90	65.77	5.46			
T0	77.64 ^a	5.17	83.05	5.90	72.23	6.14	BMI	1	0.02	
T1	71.51 ^{a,b}	5.18	70.62	5.94	72.39	6.16	CT Time	2	< 0.001	
T2	63.78 ^b	5.18	74.86 ^a	5.75	52.70 ^b	6.27	BMI * CT Time	2	0.01	
Fatigue				23.90	6.53	38.18	7.10			
T0	24.10 ^a	6.80	16.59	7.77	31.62	7.98	BMI	1	0.01	
T1	30.18 ^{a,b}	6.81	27.37	7.86	32.99	8.00	CT Time	2	0.003	
T2	38.83 ^b	6.80	27.73	7.60	49.93	8.12	BMI * CT Time	2	0.27	
Dyspnea				12.31	5.53	11.96	6.48			
T0	8.94	6.02	10.66	6.69	7.22	7.24	BMI	1	0.94	
T1	14.24	6.02	19.21	6.70	9.27	7.24	CT Time	2	0.42	

BMI, Body Mass Index; CT, Chemotherapy; HRQoL, Health Related Quality of Life; CT time: 21 days after each investigated time, always before CT (T0, day of the first CT infusion cycle; T1, day of the intermediate CT cycle; T2, day of the last CT infusion cycle); SE, Standard Error; Df, degree of freedom. BMI was categorized as "non-overweight", including those classified as underweight and eutrophic (BMI \leq 24.9 kg/m² or BMI \leq 27 kg/m², cut-off points respectively for adults and the elderly); and "overweight", including those overweight and obese (BMI \geq 25 kg/m² or $>$ 27 kg/m², respectively for adults and the elderly), considering the classification by WHO (2000) for adults and by LIPSCHTZ (1994) for elderly women. General Mixed Model (GMM): Data adjusted for age, menopausal status, income and education level. Significant Model Effects Test are in bold. Sidak test: Different superscript letters represent statistical significance when comparing pairs, p value $<$ 0.05. *Interaction between BMI and CT time. n: Value corresponding to the sum of the women on the 3 CT times (GMM analyses).

Dependent Variables	Independent Variables						Model Effects Test		
	CT Time, BMI and BMI with CT Time								
T2	13.23	6.02	7.06	6.52	19.40	7.38	BMI * CT Time	2	0.03
Insomnia			52.43	10.48	50.50	12.20			
T0	48.33	11.11	44.15	11.84	52.50	13.08	BMI	1	0.82
T1	50.49	11.11	65.79 ^a	11.95	35.19 ^b	13.16	CT Time	2	0.40
T2	55.59	11.13	47.36	11.66	63.82	13.25	BMI * CT Time	2	0.003

BMI, Body Mass Index; CT, Chemotherapy; HRQoL, Health Related Quality of Life; CT time: 21 days after each investigated time, always before CT (T0, day of the first CT infusion cycle; T1, day of the intermediate CT cycle; T2, day of the last CT infusion cycle); SE, Standard Error; Df, degree of freedom. BMI was categorized as “non-overweight”, including those classified as underweight and eutrophic (BMI ≤ 24.9 kg/m² or BMI ≤ 27 kg/m², cut-off points respectively for adults and the elderly); and “overweight”, including those overweight and obese (BMI ≥ 25 kg/m² or > 27 kg/m², respectively for adults and the elderly), considering the classification by WHO (2000) for adults and by LIPSCHTZ (1994) for elderly women. General Mixed Model (GMM): Data adjusted for age, menopausal status, income and education level. Significant Model Effects Test are in bold. Sidak test: Different superscript letters represent statistical significance when comparing pairs, p value < 0.05. *Interaction between BMI and CT time. n: Value corresponding to the sum of the women on the 3 CT times (GMM analyses).

Women with substantially increased WC (WC ≥ 88 cm), that is, at risk of metabolic complications, had a lower Physical Functioning score compared to women with WC indicative of no risk for such complications (WC < 80 cm) (p = 0.004). As for fatigue, the opposite was found, that is, those with substantially increased WC had a higher score compared to those with lower WC (WC < 80cm) (p = 0.006). In this General Mixed Model, women at the end of CT (T2) had lower scores on the Global Function (p < 0.001) and Physical Functioning (p = 0.004), and a higher Fatigue score (p = 0.010) compared to the beginning of treatment (T0). The interaction between WC and CT time had statistically significant effects on Global Health (p = 0.045) and Sexual Function (p = 0.035), and this difference was identified at T2, between those women with lower WC and those with increased WC (> 80cm); Global Function (p = 0.046) and Physical Functioning (p = 0.028), with a difference also at T2, but between women with lower WC and the others (WC > 80cm and WC > 88cm); and on Insomnia (p = 0.024), but no statistically significant difference was identified when comparing the pairs (Table 3).

Table 3

Model Effects Tests of Waist Circumference (WC) and Chemotherapy (CT) Time in the domains of Health-Related Quality of Life (HRQoL).

Dependent Variables		Independent Variables						Model Effects Test			
		CT Time, WC and WC with CT Time									
CT Time		WC (Risk of metabolic complications)						Effects	Df	p	
		No Risk		Increased Risk		Substantially Increased Risk					
		(n = 43)		(n = 40)		(n = 82)					
Mean	SE	Mean	SE	Mean	SE	Mean	SE				
Global Health			83.45	5.59	72.48	5.80	72.62	5.77			
T0	78.14	5.19	84.37	6.52	78.64	6.72	71.41	6.41	WC	2	0.07
T1	76.45	5.22	82.40	6.59	75.82	7.66	71.14	6.29	CT Time	2	0.31
T2	73.96	5.18	83.58 ^a	6.85	63.00 ^b	6.57	75.29 ^{a,b}	6.33	WC * CT Time	4	0.04
Global Function			74.75	5.27	67.88	5.48	61.86	5.49			
T0	74.66 ^a	5.01	81.64	6.40	74.89	6.65	67.46	6.25	WC	2	0.05
T1	67.79 ^{a,b}	5.02	65.22	6.51	72.28	7.57	65.87	6.18	CT Time	2	< 0.001
T2	62.03 ^b	5.01	77.39 ^a	6.75	56.46 ^b	6.49	52.25 ^b	6.17	WC * CT Time	4	0.04
Physical Functioning			83.47 ^a	5.54	72.11 ^{a,b}	5.87	64.35 ^b	5.43			
T0	79.15 ^a	5.10	88.78	6.86	78.45	7.05	70.24	6.35	WC	2	0.004

WC, waist circumference; CT, Chemotherapy; HRQoL, Health Related Quality of Life; CT time: 21 days after each investigated time, always before CT (T0, day of the first CT infusion cycle; T1, day of the intermediate CT cycle; T2, day of the last CT infusion cycle); SE, Standard Error; Df, degree of freedom. WC: Cutoff point of 80 cm was used for increased risk and 88 cm for very increased risk for metabolic complications associated with obesity (WHO, 2000). General Mixed Model (GMM): Data adjusted for age, menopausal status, income and education level. Significant Model Effects Test are in bold. Sidak test: Different superscript letters represent statistical significance when comparing pairs, p value < 0.05. *Interaction between WC and CT time. n: value corresponding to the sum of the women on the 3 CT times (GMM analyses).

Dependent Variables	Independent Variables								Model Effects Test		
	CT Time, WC and WC with CT Time										
T1	73.12 ^{a,b}	5.21	73.77	6.78	75.80	8.20	69.80	6.11	CT Time	2	0.004
T2	67.65 ^b	5.10	87.86 ^a	7.22	62.09 ^b	6.92	53.00 ^b	6.27	WC * CT Time	4	0.02
Fatigue			15.62 ^a	7.48	29.57 ^{a,b}	7.90	40.20 ^b	7.31			
T0	22.33 ^a	6.84	9.22	9.05	22.57	9.25	35.20	8.45	WC	2	0.006
T1	28.00 ^{a,b}	7.00	25.00	9.05	23.21	10.95	35.79	8.10	CT Time	2	0.01
T2	35.06 ^b	6.84	12.64	9.49	42.93	9.09	49.62	8.34	WC * CT Time	4	0.18
Insomnia			48.10	11.39	55.95	11.72	50.60	12.08	WC		
T0	47.50	10.92	40.55	13.31	45.82	13.82	56.14	13.31	CT Time	2	0.72
T1	52.24	10.88	65.29	13.41	52.85	15.13	38.58	13.23	WC * CT Time	2	0.42
T2	54.92	10.90	38.47	13.95	69.19	13.51	57.10	13.15	WC	4	0.02
Sexual Function			30.99	7.13	19.86	7.03	22.16	7.24	CT Time		
T0	23.96	6.61	27.22	7.53	21.23	7.43	23.42	7.53	WC * CT Time	2	0.06
T1	26.99	6.63	35.34	7.35	24.81	7.60	20.82	7.35	WC	2	0.05
T2	22.06	6.60	30.40 ^a	7.74	13.54 ^b	7.33	22.24 ^{a,b}	7.46	CT Time	4	0.03
<p>WC, waist circumference; CT, Chemotherapy; HRQoL, Health Related Quality of Life; CT time: 21 days after each investigated time, always before CT (T0, day of the first CT infusion cycle; T1, day of the intermediate CT cycle; T2, day of the last CT infusion cycle); SE, Standard Error; Df, degree of freedom. WC: Cutoff point of 80 cm was used for increased risk and 88 cm for very increased risk for metabolic complications associated with obesity (WHO, 2000). General Mixed Model (GMM): Data adjusted for age, menopausal status, income and education level. Significant Model Effects Test are in bold. Sidak test: Different superscript letters represent statistical significance when comparing pairs, p value < 0.05. *Interaction between WC and CT time. n: value corresponding to the sum of the women on the 3 CT times (GMM analyses).</p>											

WHR alone had no significant effect on the domains and symptoms assessed. After the end of CT (T2), there were lower scores for Physical Functioning ($p < 0.001$) and Cognitive Functioning ($p < 0.001$) and a higher score on the Symptom Scale ($p < 0.001$), compared to the beginning of CT (T0). At T2, the Physical Functioning score was significantly lower both in relation to the beginning (T0) and the intermediate treatment (T1). The interaction of WHR and CT time had statistically significant effects on Global Health ($p = 0.036$) and Insomnia ($p = 0.032$), at T1; on Physical Functioning ($p = 0.015$) and Cognitive Functioning ($p = 0.011$), at T2; and on the Symptom Scale ($p = 0.048$) and Sexual Function ($p = 0.002$), but it was not possible to identify by post-hoc at which times of CT the significance occurred (Table 4).

Table 4

Model Effects Tests of Waist-hip-ratio (WHR) and Chemotherapy (CT) Time in the domains of Health-Related Quality of Life (HRQoL).

Dependent Variables		Independent Variables				Model Effects Test				
		CT Time, WHR and WHR with CT Time								
CT Time		WHR				Effects	Df	p		
Mean	SE	Mean	SE	Mean	SE					
		No risk for metabolic complications (n = 96)		Risk for metabolic complications (n = 69)						
Global Health				75.39	4.98	82.31	5.84			
T0	79.48	5.23		80.69	5.63	78.27	6.32	WHR	1	0.13
T1	79.90	5.36		73.58 ^a	5.45	86.22 ^b	6.78	CT Time	2	0.63
T2	77.15	5.29		71.88	5.52	82.43	6.53	WHR * CT Time	2	0.03
Physical Functioning				73.80	5.03	69.18	6.09			
T0	77.83 ^a	5.40		81.66	5.90	74.00	6.74	WHR	1	0.36
T1	73.99 ^a	5.55		69.57	5.68	78.41	7.27	CT Time	2	< 0.001
T2	62.65 ^b	5.46		70.17 ^a	5.76	55.12 ^b	7.00	WHR * CT Time	2	0.01
Cognitive Functioning				64.03	7.62	62.92	8.82			
T0	71.56 ^a	8.11		70.58	8.75	72.54	9.74	WHR	1	0.86
T1	65.77 ^{a,b}	8.29		59.03	8.47	72.51	10.42	CT Time	2	< 0.001
T2	53.09 ^b	8.18		62.47 ^a	8.58	43.70 ^b	10.05	WHR * CT Time	2	0.01
Symptom Scales				27.20	4.50	30.33	5.23			
T0	24.74 ^a	4.81		20.33	5.20	29.16	5.79	WHR	1	0.43

WHR, Waist-to-Hip ratio; CT, Chemotherapy; HRQoL, Health Related Quality of Life; CT time: 21 days after each investigated time, always before CT (T0, day of the first CT infusion cycle; T1, day of the intermediate CT cycle; T2, day of the last CT infusion cycle); SE, Standard Error; Df, degree of freedom. WHR: A cut-off point ≥ 0.85 was used for risk of metabolic complications (WHO, 2000). General Mixed Model (GMM): Data adjusted for age, menopausal status, income and education level. Significant Model Effects Test are in bold. Sidak test: Different superscript letters represent statistical significance when comparing pairs, p value < 0.05 . *Interaction between WHR and CT time. n: value corresponding to the sum of the women on the 3 CT times (GMM analyses).

Dependent Variables			Independent Variables				Model Effects Test		
			CT Time, WHR and WHR with CT Time						
T1	26.87 ^{a,b}	4.93	31.14	5.05	22.60	6.29	CT Time	2	< 0.001
T2	34.68 ^b	4.86	30.12	5.10	39.24	5.98	WHR * CT Time	2	0.04
Insomnia			54.97	10.04	39.87	11.51			
T0	47.15	10.61	45.99	11.36	48.30	12.57	WHR	1	0.07
T1	41.69	10.83	59.82 ^a	11.04	23.55 ^b	13.42	CT Time	2	0.23
T2	53.42	10.70	59.08	11.16	47.76	12.96	WHR * CT Time	2	0.03
Sexual Function			24.38	6.84	27.19	7.44			
T0	26.03	6.90	24.16	7.08	27.90	7.55	WHR	1	0.51
T1	27.12	6.97	29.35	6.96	24.88	7.77	CT Time	2	0.33
T2	24.20	6.94	19.61	7.04	28.78	7.75	WHR * CT Time	2	0.002
<p>WHR, Waits-to-Hip ratio; CT, Chemotherapy; HRQoL, Health Related Quality of Life; CT time: 21 days after each investigated time, always before CT (T0, day of the first CT infusion cycle; T1, day of the intermediate CT cycle; T2, day of the last CT infusion cycle); SE, Standard Error; Df, degree of freedom. WHR: A cut-off point ≥ 0.85 was used for risk of metabolic complications (WHO, 2000). General Mixed Model (GMM): Data adjusted for age, menopausal status, income and education level. Significant Model Effects Test are in bold. Sidak test: Different superscript letters represent statistical significance when comparing pairs, p value < 0.05. *Interaction between WHR and CT time. n: value corresponding to the sum of the women on the 3 CT times (GMM analyses).</p>									

In the General Mixed Model involving the WHtR, we identified that CT time had a statistically significant effect on the Role Functioning score ($p = 0.047$), although the comparison of pairs by the Sidak Test was not able to detect at what times that difference occurred. The interaction between WHtR and CT time had statistically significant effects on Role Functioning ($p = 0.030$) at T2 and on the Global Function ($p = 0.018$), Physical Functioning ($p = 0.014$) and Fatigue ($p = 0.033$), with no statistically significant difference by post-hoc in these last three domains. (Table 5). Considering that Emotional Functioning, Social Functioning, Pain, Body Image and Sexual Satisfaction did not present statistical significance in any of the General Mixed Models tested, these domains and symptoms were tested only for the influence of CT time. At the end of CT (T2), women had a lower Social Functioning score ($p = 0.043$) and a higher Pain score ($p = 0.010$), compared to the beginning of treatment (T0) (Table 6).

Table 5

Model Effects Tests of Waist-height ratio (WHtR) and Chemotherapy (CT) Time in the domains of Health-Related Quality of Life (HRQoL).

Dependent Variables		Independent Variables						Model Effects Test		
		CT Time, WHR and WHtR with CT Time								
CT Time		WHtR				Effects	Df	p		
		No Excess Abdominal Fat (n = 15)		Excess Abdominal Fat (n = 149)						
Mean	SE	Mean	SE	Mean	SE					
Global Function				68.78	7.80	69.77	5.42			
T0	75.41	6.30		74.26	10.26	76.56	5.83	WHtR	1 0.90	
T1	63.06	6.30		54.26	10.26	71.86	5.82	CT Time	2 0.14	
T2	69.35	6.30		77.82	10.26	60.88	5.82	WHtR * CT Time	2 0.01	
Physical Functioning				69.64	8.70	73.02	5.63			
T0	76.77	6.73		74.08	11.25	79.47	6.08	WHtR	1 0.72	
T1	65.00	6.73		54.08	11.25	75.92	6.07	CT Time	2 0.23	
T2	72.21	6.73		80.75	11.25	63.67	6.07	WHtR * CT Time	2 0.01	
Role Functioning				69.67	11.13	63.93	7.95			
T0	80.35	9.66		79.67	15.81	81.04	8.74	WHtR	1 0.63	
T1	57.88	9.66		49.67	15.81	66.09	8.73	CT Time	2 0.04	
T2	62.16	9.66		79.67 ^a	15.81	44.66 ^b	8.73	WHtR * CT Time	2 0.03	
Fatigue				29.05	12.32	33.56	7.92			
T0	25.06	9.18		23.13	15.22	26.99	8.43	WHtR	1 0.73	
T1	38.89	9.18		47.57	15.22	30.21	8.42	CT Time	2 0.29	
T2	29.97	9.18		16.46	15.22	43.48	8.42	WHtR * CT Time	2 0.03	

WHtR, Waist-to-Height ratio; CT, Chemotherapy; HRQoL, Health Related Quality of Life; CT time: 21 days after each investigated time, always before CT (T0, day of the first CT infusion cycle; T1, day of the intermediate CT cycle; T2, day of the last CT infusion cycle); SE, Standard Error; Df, degree of freedom. WHtR: A cutoff point ≥ 0.5 was used for excess abdominal fat (ASHWELL; HSIEH, 2005). General Mixed Model (GMM): Data adjusted for age, menopausal status, income and education level. Significant Model Effects Test are in bold. Sidak test: Different superscript letters represent statistical significance when comparing pairs, p value < 0.05 . *Interaction between WHtR and CT time. n: value corresponding to the sum of the women on the 3 CT times (GMM analyses).

Table 6
Model Effects Tests of Chemotherapy (CT) Time in the domains of Health-Related Quality of Life (HRQoL).

Dependent Variables	T0		T1		T2		Df	p
	Mean	SE	Mean	SE	Mean	SE		
Emotional Functioning	66.68	8.52	65.14	8.52	61.28	8.52	2	0.41
Social Functioning	88.09 ^a	6.93	80.37 ^{a,b}	6.93	76.98 ^b	6.93	2	0.04
Pain	21.75 ^a	10.27	28.54 ^{a,b}	10.27	41.81 ^b	10.27	2	0.01
Body Image	84.44	10.29	83.98	10.29	78.68	10.29	2	0.13
Sexual Satisfaction	74.11	8.20	61.48	7.56	59.74	7.77	2	0.12

CT, Chemotherapy; HRQoL, Health Related Quality of Life; CT time: 21 days after each investigated time, always before CT (T0, day of the first CT infusion cycle; T1, day of the intermediate CT cycle; T2, day of the last CT infusion cycle); SE, Standard Error; Df, degree of freedom. Only the domains and symptoms that had no effect of the anthropometric variable and, or its interaction with the CT time, were tested. General Mixed Model (GMM): Data adjusted for age, menopausal status, income and education level. Significant Model Effects Test are in bold. Sidak test: Different superscript letters represent statistical significance when comparing pairs, p value < 0.05.

4. Discussion

Through this present study, we identified the effect of chemotherapy time, nutritional status and also the interaction between the chemotherapy time and the nutritional status of women with BC on the domains and symptoms of HRQoL. Overweight women; WC indicative of increased risk and substantially increased risk of metabolic complications; WHR indicative of risk of developing chronic diseases; WHtR indicative of excess abdominal fat; that is, women with a worse nutritional status or on a more advanced time of treatment (T1 and T2) presented worse scores on important domains of HRQoL. It is important to highlight that the nutritional status, in isolation, had a statistically significant effect, demonstrating the importance of seeking a healthy nutritional status to minimize the negative impact on HRQoL during the treatment. We also observed that overweight, higher WC and WHtR and the interaction with CT time negatively impacted the global function, that is, they presented a worse quality of life and physical condition at the end of the treatment (T2 ≠ T0).

Women with BC, when compared with the population free of the disease, show a decrease in HRQoL [12]. Added to that, antineoplastic treatments are also associated with a HRQoL decrease [25].

Besides that, we identified a decrease in the scores of physical function, which was associated with higher levels of BMI, WC, WHR, WHtR and longer CT times. Factors related to the disease and treatment such as cardiotoxicity, neurotoxicity, lymphedema, precocious menopause, sexual dysfunction, infertility, secondary leukemia, weight gain, difficulty sleeping and fatigue can justify the negative impact on HRQoL and physical function [26]. Added to that, there is the fact that a worse nutritional status, characterized by BMI, WC, WHR, WHtR measures, can be associated with a worsening physical function, as identified by Mosher et al, 2009, where an association with BMI was found. Mosher et al (2009) also identified that better diet quality and exercise are associated with better physical function (better vitality and physical function $p \leq 0.05$) [27].

We also observed a significant impact of the interaction of CT time and higher levels of BMI, WC and WHR on the insomnia score.. Among the factors that can be related to this problem, it is the presence of menopause symptoms caused by CT or hormonal therapy such as hot flashes [28] and also biological modifications related to the cancer and treatment, which includes changes in pro-inflammatory cytokines and the hypothalamic-pituitary-adrenal axis (HPA) [29].

Sexual function was also significantly impacted by the interaction between CT time and higher WC and WHR.. A study by Biglia et al. (2010)[30] evaluated the impact of BC treatment on sexual function, cognitive function and body weight on pre-menopause women, and identified that at T0 (baseline, first week after the surgery) 77.1% of the sample (n = 35) reported sexual activity during the 4 previous weeks, which reduced to 37.1% at T1 (after the adjuvant CT or after at least 6 months of hormonal therapy) and to 34.3% at T2 (one year after surgery). It also became evident in Biglia et al (2010) study, that they had a weight gain (T0 = 65.19; T1 = 67.26; T2 = 67.21) with a difference of + 2.07 between T0 and T1 (p = 0.035) and + 2.02 between T0 –T2 (p = 0.049) [30].

Higher BMI and CT time, as well as the interaction of WHtR with CT time, impacted negatively on the fatigue score. Among the factors that can be related to this problem it is that, BMI and CT are associated with the increase of receptor two of tumoral necrosis factor (TNF-RII), which has been related to higher fatigue scores [31]. The TNF-RII is a receptor of the alfa tumoral necrosis factor (TNF- α), an inflammatory mediator [32]. A study performed on mice found that the adipose tissue is related with the production of TNF- α [33] and obese humans have a higher production of this cytokine than normal weight individuals [34].

We also identified a decrease in the physical function score, associated with higher BMI and WC, longer CT time and the interaction between BMI, WC, WHR and WHtR with CT time. Nutritional status influences the HRQoL not just on BC, but also on colorectal cancer; an elevated WC is also associated with a worse physical function and higher scores of fatigue in men and women [35]. CT time also influences the HRQoL of these women, worsening the social function domain.. Among the factors that could be related to this issue, is the possible occurrence of nausea and vomiting due to CT [36]..

Pain was also affected by CT time, where the score worsened throughout the treatment. The mechanisms involved in the pain process are not very clear, but it is known that CT acts on nociceptors and glia modulators, activating the microglia and astrocytes of the spinal medulla, and these release neuromodulators related to pain, causing chronic pain [37].

In the face of the shown facts, it becomes clear the need to reinforce the improvement of changeable factors that can increase the survival of these women, through a healthy diet, regular physical activity, and consequently an adequate nutritional status, with the purpose of achieving a better HRQoL, because CT itself already causes an 0.55 odds ratio of mortality in 10 years [38].

A systematic review that included 63 studies randomized 5761 women in two groups, one intervention (physical activity, n = 3239) and the other control (n = 2524), revealed that the physical activity intervention resulted in small to moderated improvements in HRQoL, emotional function, self reported and measured physical function, anxiety, cardiorespiratory capability and fatigue. However, these results must be interpreted carefully because the quality of evidence is small to moderated, due to heterogeneity of the interventions and measure of results [26].

The study of Phillips et al (2015)[39], also demonstrated that maintaining or increasing physical activity during the post diagnosis time was significantly and independently associated with lower fatigue, depression and stress scores and higher values for physical well-being, physical, social, emotional and functional scores, specific to BC and global HRQoL (effect size = 0.23 a 0.60). Maintaining or losing weight had an independent association (p < 0.05) with lower fatigue, higher physical well-being specific for BC and general HRQoL (effect size = 0.28 a 0.87).[39].

With regard to food intake, the dietary pattern is a factor of influence on HRQoL of BC survivors, and the ones with a healthier diet, have a better HRQoL, presenting better role function, emotional function, cognitive function, social function and global health status [10]. Assaf et al (2016) verified that a change in diet, with a reduction of 20% of daily calories in fat, eating fruits and vegetables 5 times per day and grains 6 times per day, caused an improvement in HRQoL[40] and a better HRQoL is associated with a better overall survival after 1 year of diagnosis [41] .

It becomes evident that modifications in changeable lifestyle factors directly affect the nutritional status, and consequently, can achieve significant improvements in HRQoL. Furthermore, it has the potential to contribute to a better prognosis [42] and a lower mortality rate in 10 years [38].

About the possible limitations of this study, it is important to consider that BMI is a method to classify the nutritional status of individuals, but is acknowledged that it is a limited method, and there may be overestimation or underestimation of the real nutritional condition. Even though, we highlight that all the measurements, including interviews, were performed by trained nutritionist.

Considering the fact that there are only a few articles in the literature that have investigated the relationship between nutritional status and HRQoL, we highlight the contribution of these results, especially because this is the first prospective study analyzing the effects the association between nutritional status and CT time has on HRQoL of BC women.

5. Conclusion

It was verified that a worse nutritional status (overweight, increased and substantially increased WC, high WHR and high WHtR) and longer CT time (T1 and T2) are associated with worse mean scores of symptoms and HRQoL domains. Therefore, it is relevant to encourage BC women undergoing CT to have a healthier diet and regularly practice exercise, with the purpose of maintaining an adequate nutritional status. The improvement of these modifiable factors during CT can contribute to a better HRQoL, better adherence to the treatment, better prognosis and for higher overall and disease free survival rates.

Declarations

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Competing interest

The authors declare that they have no competing interest.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Authors' contribution

AMM and IDDC equally contributed to this article. Conceptualization, AMM, IDDC, ECM, CEP and YCPM; Formal analysis, AMM, IDDC, FSM, MAF and YCPM; Funding acquisition, CEP and YCPM; Investigation, AMM, IDDC, FSM, MAF, ECM and YCPM; Methodology, AMM, IDDC, ECM, CEP and YCPM; Project administration, YCPM; Resources, YCPM; Supervision, CEP and YCPM; Visualization, AMM, IDDC and YCPM; Writing – original draft, AMM, IDDC, FSM, MAF and YCPM; Writing – review & editing, AMM, IDDC, FSM, MAF, ECM, CEP and YCPM. All authors read and approved the final manuscript.

Ethics approval

This study was approved by the Ethics Committee on Research with Human Beings of Federal University of Uberlândia (no. 721,977/14, adhering no. 1,111,998/15) and complies with the principles and ethical standards of the Declaration of Helsinki and CNS Resolution 466/12.

Consent to participate

All the participants signed informed consent.

Consent for publication

Not applicable.

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