Effect of adjuvant antineoplastic treatment on body weight change in women with breast cancer

Efeito do tratamento antineoplásico adjuvante na mudança de peso corporal em mulheres com câncer de mama

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Study supported by grants from Conselho Nacional de Desenvolvimento Cientifico e Tecnológico (CNPq) – Edital MCT/CNPq 14/2008.

ABSTRACT

Aims: To identify the effect of adjuvant antineoplastic treatment on body weight change of women with breast cancer.

METHODS: A non-randomized clinical study included women with a recent surgical diagnosis of breast cancer, admitted to the *Maternidade Carmela Dutra* hospital in Florianópolis, Santa Catarina, southern Brazil, between October 2006 and July 2008. Food intake, weight, body mass index, hip circumference, waist circumference and other variables were measured before (baseline) and after the adjuvant antineoplastic treatment (pos-treatment). A mixed effects linear regression model was used to estimate the longitudinal changes occurring in weight.

Results: The sample comprised 53 patients. A significant increase (P<0.05) was observed in body weight (2.81 kg), body mass index (1.08 kg/m^2), hip circumference (3.62 cm) and waist circumference (1.93 cm). In relation to diet, there was a significant increase (P<0.05) in the intake of energy (272.7 kcal), total fat (11.2 g) and polyunsaturated fatty acids (5.4 g). The final regression model for the change in body weight demonstrated that the women who were exposed to chemotherapy treatment, and to chemotherapy associated with radiotherapy, had the largest mean increase in body weight (2.47 kg and 5.21 kg, respectively). Socio-economic, demographic and nutritional factors were not associated with the increase in body weight.

Conclusions: Weight gain was associated with chemotherapy treatment either alone or in combination with radiotherapy.

KEY WORDS: BODY MASS INDEX; WAIST CIRCUMFERENCE; ANTINEOPLASTIC THERAPY PROTOCOLS; BREAST CANCER; CLINICAL TRIAL.

RESUMO

Objetivos: Identificar o efeito do tratamento antineoplásico adjuvante sobre a mudança de peso corporal em mulheres com câncer de mama.

Métodos: Um estudo clínico não randomizado incluiu mulheres com diagnóstico cirúrgico recente de câncer de mama, admitidas no hospital Maternidade Carmela Dutra em Florianópolis, Santa Catarina, entre outubro de 2006 e julho de 2008. Os dados de consumo alimentar, peso corporal, índice de massa corporal, circunferência do quadril, circunferência da cintura e outras variáveis, foram avaliados antes (basal) e depois do tratamento antineoplásico adjuvante (pós-tratamento). Um modelo de regressão linear de efeitos mistos foi utilizado para estimar as mudanças longitudinais que ocorreram no peso corporal.

Resultados: A amostra foi composta por 53 pacientes. Foi observado um aumento significativo (P<0,05) no peso corporal (2,81 kg), índice de massa corporal (1,08 kg/m^2), circunferência do quadril (3,62 cm) e circunferência da cintura (1,93 cm). Em relação aos aspectos dietéticos, houve um significativo aumento (P<0,05) na ingestão de energia (272,7 kcal), gorduras totais (11,2 g) e ácidos graxos poliinsaturados (5,4 g). O modelo final para a mudança no peso corporal demonstrou que as mulheres as quais foram expostas ao tratamento quimioterápico, e quimioterápico associado ao radioterápico, tiveram um maior aumento médio no peso corporal (2,47 kg e 5,21 kg, respectivamente). Os fatores socioeconômicos, demográficos e nutricionais não foram associados com o aumento no peso corporal.

Conclusões: O aumento de peso esteve associado com o tratamento quimioterápico sozinho ou em combinação com o tratamento radioterápico.

DESCRITORES: ÍNDICE DE MASSA CORPORAL; CIRCUNFERÊNCIA DA CINTURA; PROTOCOLOS DE QUIMIOTERAPIA ANTINEOPLÁSICA; CÂNCER DE MAMA; ENSAIO CLÍNICO.

Received: February 2012. Accepted: May 2012

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INTRODUCTION

An increase in body weight is one of the main problems faced by women in the first year after a diagnosis of breast cancer.[1-3] This increase in weight may be progressive and prolonged, lasting for more than a year after the end of treatment.[4] Besides playing an important role in the etiology of breast cancer,[5] weight gain during or after adjuvant treatment has been associated with an increased risk of recurrence and co-morbidities.[1,6]

Scientific evidence for a role of diet in the recurrence of breast cancer is largely inconclusive. Recent studies that support the International Guidelines which provide targeted recommendations for women at risk of the recurrence of breast cancer and also attempt to prevent co-morbidities as a consequence of treatment, have proposed three final recommendations which are to: limit exposure to alcohol, moderate calorie intake and, most importantly, adhere to a balanced diet (especially postmenopausal women) to avoid weight gain.[7]

After breast cancer diagnosis, a body weight gain is a common and clinically well-known phenomenon. Although the reason for this body weight gain has still not been well established, adjuvant chemotherapy treatment seems to be a major determinant.[8, 9] Adjuvant chemotherapy has been found to be a strong clinical predictor of weight gain in women with early-stage breast cancer, which is independent of age, nodal status, body mass index (BMI) and reported calorie intake at diagnosis.[10, 11] Further observations need to be made regarding factors associated with weight gain in breast cancer patients from the epidemiological point of view.[7,12]

Considering that the effects of antineoplastic treatment for breast cancer and the association between certain factors and weight gain during chemotherapy are not well understood, the objective of this study was to identify the effect of adjuvant antineoplastic treatment on body weight change of women with breast cancer.

METHODS

A non-randomized clinical trial was conducted on women with a recent surgical diagnosis of breast cancer, admitted to the *Maternidade Carmela Dutra* hospital in Florianópolis, Santa Catarina, southern Brazil, between October 2006 and July 2008. All subjects underwent surgery and adjuvant treatment (namely, chemotherapy and/or radiotherapy and/or immunotherapy) prior to February 2009. This study was approved by the Ethics Committee of Human Research at the *Maternidade Carmela Dutra* and at the *Universidade Federal de Santa Catarina* (N. 099/08). All participants gave written informed consent.

Data collection was performed in the pre-surgery phase (baseline) and after the end of the adjuvant treatments for breast cancer (post-treatment). During the interviews, socio-economic, demographic, clinical, anthropometric and food intake information was obtained. Information relating to the treatment was obtained at the end of the study.

In post-treatment phase, in addition to the loss of women who were not located, women who reported energy consumption below the basal energy expenditure,[13] characterized as under-reporting, were excluded from the study.[14]

Information requested included personal details, clinical history, physical activity and socio-economic data, all based on previous studies.[15-17] Anatomopathological staging of the disease was performed according to the TNM Classification of Malignant Tumours proposed by the Union for International Cancer Control.

Weight (kg) and height (m) data were obtained using a Filizola® anthropometric mechanical scale (Filizola S/A, São Paulo, Brazil). The body weight and height were measured according to standard procedures and the results were used to calculate BMI.[18, 19] Waist circumference (WC) and hip circumference (HC) were measured according to standard procedures and were used to calculate the waist-to-hip ratio (WHR).[19] The cut-off points used for classification and definition of risk in women in the study were WC $\geq$ 88 cm (National Institutes of Health/National Heart, Lung and Blood Institute, 1998)[20] e WHR $\geq$ 0.85 (World Health Organization, 2000).[19]

In order to assess physical activity, patients were questioned whether they practiced physical exercises. If so, what types of physical activities, how many times a week, how many minutes and also how long they exercise. Usual dietary intake was obtained with a previously validated food frequency questionnaire.[21] Dietary data were collected retrospectively, with the food consumption reported at baseline referring to the preceding year and the end of the study referring to the post-surgical period up to the date of the interview.

The participants determined the portion's size of each food item consumed with the assistance of an album containing color photographs of foods[22] or household measures of different sizes commonly used. The size described was then transformed into grams or millilitres.[23] From information on nutritional composition of each food item,[24, 25] food intake was estimated in relation to daily energy (Kcal), protein, carbohydrate, total fat, saturated fatty acids, monounsaturated fatty

acids, polyunsaturated fatty acids, cholesterol and fiber.

The study variables were classified as: a) clinical and cancer-related variables (anatomopathological stage, axillary lymph node status, tumour size, hormone therapy, chemotherapy and radiotherapy); b) variables related to individuals (age, schooling, menopausal status, physical activity and *per capita* income); c) anthropometric variables; and d) dietary intake variables.

Sample size (n=53) allowed to detect differences of 2.0±4.5 kg in the mean body weight, with 95% confidence level and 80% power test. Data analysis was carrying out with *Stata* software, version 9.0 (Stata Corporation), and 5% was considered the significance level.

Categorical variables were described through frequencies. Shapiro Wilk test was used to evaluate the normality of continuous variables that were described by means and medians. Student's paired *t*-test was used to compare means. Wilcoxon test was used to compare medians. Primary outcomes are to be measured changes from pretreatment to post treatment in weight gain. Longitudinal changes in body weight were estimated by the mixed linear regression model described by Rabe-Hesketh and Skrondal (2005).[26] The age variable was used as a marker of the time elapsed between the interviews and, as a result, was maintained in the final model. Variables that presented a value of $P<0.25$ in the univariate linear regression were included in the analysis of mixed effects.

In the construction of the model, variables with more than two categories were transformed into dummy (fictitious) variables and those that presented low frequency and colinearity were excluded from the analysis. Construction of the final linear regression model of mixed effects followed the backward process. The models were selected using Akaike's information criterion. The need to include random effects in the variable age was assessed using the test of restricted maximum likelihood ratio. Variability of the data obtained from linear regression of mixed effects was estimated from the intraclass correlation coefficient of the model. The *xtmixed* function was used to determine the estimates.

RESULTS

The sample comprised 53 patients. Mean age of the participants at baseline was 52.5±10.6 years and at the end of the study was 53.6±10.5 years. Mean interval of time between interviews was approximately 12 months.

Most women were caucasian (92.5%), 67.9% had formal education of less than eight years, and 83% declared a monthly *per capita* income of two Brazilian minimum salaries (equivalent to USD $300.67) or less.

There was a preponderance of invasive carcinoma (92.5%), and 56.7% of the women had tumours no larger than 2 cm. In 60.4% of the women the axillary lymph nodes were not involved. TNM staging showed that 73.5% of the women were between stages I and II. In relation to the treatment, 94.3% received adjuvant treatment based on chemotherapy and/or radiotherapy, and 77.4% of these subjects underwent hormone therapy at some time (Table 1).

Table 1. Clinical data on 53 women in treatment for breast cancer, in Florianópolis, Santa Catarina State, Brazil.

Clinical and treatment variables	N	%
Tumour classification*		
Infiltrating carcinoma	49	92.5
Carcinoma *in situ*	4	7.5
Tumour Size (T)		
Not defined	1	1.8
0.1 – 2	30	56.7
2.1-5	21	39.7
>5	1	1.8
Tumour stage†		
0	3	5.7
I	21	39.6
IIA	11	20.7
IIB	7	13.2
IIIA,B,C	11	20.8
Axillary lymph nodes involvement		
Positive	21	39.6
Negative	32	60.4
Treatments completed		
Chemotherapy	15	28.3
Radiotherapy	14	26.4
Radiotherapy associated with Chemotherapy	21	39.6
Not exposed to chemotherapy and radiotherapy	3	5.7
Hormone therapy		
Tamoxifen	34	64.2
Aromatase inhibitor	7	13.2
No hormonal medication	12	22.6

* Only adenocarcinom were included, with no distinction applied to different histological types of carcinoma.
† Tumour stage was determined according to International Union Against Cancer.

With regarding to menopausal status, 52.8% reported being in menopause at the time of diagnosis and 24.6% entered menopause while undergoing adjuvant treatment; 33.3% of the menopausal women were using or had used hormone replacement therapy.

In relation to physical activity, 26.4% of the subjects took part in some form of physical exercise at baseline. We found that two women (3.8%) had stopped exercising at the end of the study, while 13 (24.5%) took up some kind of physical activity during this period.

Regarding the nutritional status, 30.2% were eutrophic, 37.7% were overweight and 32.1% were obese. A value of WC ≥88 cm was observed in 49% of the subjects and the WHR was ≥0.85 in 45.3% of cases at baseline.

A significant increase in body weight, BMI, HC, and WC measurements was observed at the end of the study. We found that 73.6% (n=39) of the patients gained weight and 56.6% of these women gained 2 kg or more. Significant increases were found to be 2.81 kg for body weight, 1.08 kg/m^2 for BMI, 1.93 cm for WC and 3.62 for HC, without affecting the WHR. Also, a significant increase in the energy intake (272 kcal) increased consumption of total fat (11.2 g), and specifically polyunsaturated fatty acids (5.4 g), were observed (Table 2).

After the univariate analysis, the variables chemotherapy (p=0.02), radiotherapy associated with chemotherapy (p<0.0005), tamoxifen and aromatase inhibitor treatments (p=0.002), 9-11 years of education (p=0.18), post menopause (p<0.0005), physical activity (p=0.08), energy (p=0.05), lipids (p=0.05) and carbohydrate intake (p=0.04) were selected for construction of the final linear regression model for weight.

The patients exposed to chemotherapy and chemotherapy plus radiotherapy were found to have a mean increase in body weight of 2.47 kg and 5.21 kg, respectively, over the period of follow-up. The women who underwent radiotherapy alone or those who were not exposed to chemotherapy or radiotherapy showed no significant increase in body weight over time (Table 3 and Figure 1).

Table 2. Changes in body weight, body mass index, waist circumference, hip circumference, waist to hip ratio and nutrients intake before (baseline) and after treatment (post-treatment) in 53 women with breast cancer, in Florianópolis, Santa Catarina state, Brazil.

	Baseline Mean±SD Median	**Post-treatment Mean±SD Median**	**Difference Mean±SD Median**	***P***
Current weight (kg)	70.1±13.1 69.1	73.0±14.9 72	2.81±4.37 2.09	0.0000[2]
Body mass index (kg/m^2)	28.0±4.8 27.33	29.12±5.3 28.47	1.08±1.62 0.85	0.0000[2]
Waist circumference (cm)	89.69±13.3 87.0	91.63±13.6 89.0	1.93±5.43 1.0	0.0124[2]
Hip circumference (cm)	103.9±9.6 104.0	107.5±10.4 106.0	3.62±4.86 3.0	0.0000[2]
Waist/hip ratio (cm)	0.86±0.98 0.84	0.84±0.69 0.85	-0.01±0.07 -0.003	0.2071[1]
Energy (kcal/day)	2.472±726 2303	2.744±825 2703	272±753 291	0.0266[1]
Protein (g/day)	92.9±24 91.3	102.6±31.4 100	9.7±31.8 2.65	0.0689[1]
Carbohydrate (g/day)	342.3±121.5 327.1	375.5±152.9 345.2	33.2±121 15.0	0.1043[1]
Lipids (g/day)	80.4±23.3 79.2	91.7±29.1 88.9	11.2±31.6 6.07	0.0121[2]
Saturated fatty acids (g/day)	24.4±9.3 24.1	26.5±11.1 24.7	2.1±10.8 0.2	0.1627[2]
Monounsaturated fatty acids (g/day)	22.5±7.8 21.3	25.2±10.0 23.0	2.6±9.7 0.9	0.0497[2]
Polyunsaturated fatty acids (g/day)	17.9±6.25 16.4	23±9.2 21.8	5.4±9.5 4.9	0.0001[2]
Cholesterol (mg/day)	266.9±118.3 269.0	311±179.3 269.0	44.3±183.9 3.4	0.3368[1]
Fiber (g/day)	28.5±11.8 27.9	31.7±16.0 28.2	3.2±13.4 3.8	0.0934[1]

[1] Wilcoxon paired data test.
[2] Student's paired *t* test.
SD: standard deviation.

Table 3. Final model of mixed effects linear regression for body weight gain in 53 women after treatment for breast cancer, Florianópolis, Santa Catarina state, Brazil.

Variables	β	Standard deviation	95% CI	*p*
Intercept	66.42	2.76	61.01-71.84	**<0.0005**
Age (years)*	0.07	0.04	-0.002-0.14	0.06
Radiotherapy	0.17	1.06	-1.914-2.25	0.88
Chemotherapy	2.47	1.00	0.50-4.44	**0.01**
Radio + chemotherapy	5.21	0.86	3.53-6.89	**<0.0005**
Not exposed to radio/ chemotherapy	-0.10	2.24	-4.49-4.29	0.96
Random Effects				
Intercept	13.75	1.38	11.31-16.75	
Residual	2.77	0.28	2.27-3.38	
Measurements (n)	106			
Groups (n)	53			

* The age variable was used as a marker of the time elapsed between the interviews and was maintained.
β: Coefficient estimates.
CI: confidence interval.

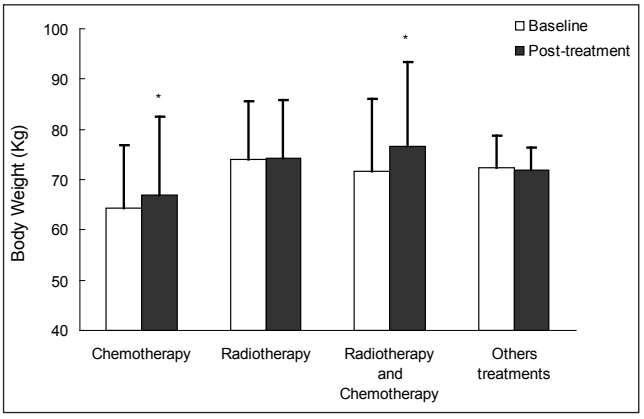

Figure 1. Effect of different adjuvant treatments for breast cancer on body weight. Body weight (kg) baseline and post-treatment with Chemotherapy (n=15), Radiotherapy (n=14), Radiotherapy and Chemotherapy (n=21) or others treatments (n=3). * $p<0.05$ compared to corresponding period baseline (Paired Student's *t*-test).

DISCUSSION

The results of this study confirm the effect of chemotherapy on body weight change during the treatment of breast cancer, as previously reported.[8-11] Adjuvant chemotherapy is a strong clinical predictor of weight gain in women with early-stage breast cancer which is independent of age, nodal status, BMI, and reported caloric intake at diagnosis.[10] Several but not all patients experience weight gain during adjuvant treatment for breast cancer.[4]

We observed an increase in energy consumption, probably due to increased consumption of total fat (11.2 g), specifically polyunsaturated fatty acids (5.4 g), and an increase of the measures of circumferences (HC and WC), body weight, and BMI. These results may be possible risk factors for the recurrence of breast cancer.[27] A meta-analysis that evaluated the relationship between the consumption of fat and breast cancer concluded that a high fat intake increases the risk of breast cancer by 13%, regardless of whether it is saturated or unsaturated fat.[28] Although it is important to note that the food frequency questionnaire has limitations regarding adequate levels of energy and nutrients,[29] it is nevertheless a suitable instrument for determining the usual diet in individuals with chronic disease during breast cancer treatment.

In the univariate regression the following variables were selected as predictive factors for weight gain: tamoxifen treatment, aromatase inhibitor treatments, years of education, postmenopause, energy intake, lipids intake, carbohydrate intake and physical activity. However, these relationships were not sufficient to explain the weight gain in the final model. As in our study, in other studies with representative samples and with appropriate control of confounding factors associated with weight gain during breast cancer treatment, no association has been observed with tamoxifen and aromatase inhibitor treatments, years of education, menopause, or physical activity. However strategies to modify these behaviors are likely to influence the long-term pattern of weight change.[9,30-35]

In the results for the linear regression of mixed effects the women exposed to chemotherapy or chemotherapy combined with radiotherapy exhibited mean increases in body weight of 2.47 kg and 5.21 kg, respectively. This finding is in agreement with the observations of other authors who have verified an increase in body weight associated with adjuvant therapies for breast cancer.[6,9,30] It has been reported that

the weight gain during chemotherapy can vary between 2.5 and 6.2 kg, and can occur in 50 to 70% of women treated for breast cancer.[31]

As demonstrated in our study, significant increases of 6.6% and 3.6% of weight were noted in women undergoing the treatment set of chemo-radiotherapy and chemotherapy alone, respectively, compared to radiotherapy (0.7%). Frequently, other studies have considered absolute weight gain,[4,30] however, relative weight gain is a better measure since it considers the potential confounding factors associated with initial body weight.[32] Another frequent criticism is the absence of a control group for comparison, in order to investigate whether subjects who did not receive chemotherapy could have a similar weight change.[30]

One of the limitations of this study is the sample size, and this inhibits adjustment for possible confounding factors related to weight change, such as age, BMI, race, education, energy intake, and physical activity.[32] However, despite this limitation our results are consistent with those of studies of large impact, where chemotherapy is the main predictor of weight gain.[33] The fact that in the present study we did not observe the effect of other variables on body weight may be explained by the size of the sample, which did not allow the identification of differences in the variables that in a given category presented a low frequency and had to be excluded. Finally, further limitation was the lack of assessment of duration of treatment, number of cycles of chemotherapy, and concentrations and types of chemotherapy agents, as well as other associated drugs. However, as in the case of physical activity, this was not the focus of the study. Bearing in mind the potential role of physical activity in regulating the weight gain of the women while undergoing breast cancer therapy, this variable should be studied in greater detail in future research.

In conclusion, this study showed that women gained weight after diagnosis and during adjuvant treatment for breast cancer, and that this weight gain was associated with chemotherapy treatment, either alone or in combination with radiotherapy. Future research involving this population should focus on behaviour and other factors involved in weight gain, and treatment regimes should also be examined. In addition, duration of the investigation should be extended for a period beyond the end of the treatment.

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