 Variations in the body mass index in Brazilian women undergoing adjuvant chemotherapy for breast cancer

**Abstract**

**PURPOSE:** To evaluate variations in the body mass index in patients undergoing adjuvant chemotherapy for breast cancer, and to associate these changes with patient's age and adjuvant chemotherapy regimen. **METHODS:** We performed a retrospective cohort study in order to correlate any variation in the body mass index before and after adjuvant chemotherapy with patient's age and adjuvant chemotherapy regimen. Patients who received any form of prior hormone therapy, such as tamoxifen or aromatase inhibitors, were excluded. We selected data for 196 patients with stage I to III breast cancer who were treated by radical or conservative surgery and received adjuvant chemotherapy at the Cancer Institute of the State of São Paulo, Brazil. **RESULTS:** Before adjuvant chemotherapy, 67.8% of patients were classified as overweight or obese according to their body mass indices. Around 66.3% (95% CI 59.7–73.0) of the patients exhibited an increase in the body mass index after adjuvant chemotherapy. The average age of all patients was 56.3 ± 11.3 years. Participants whose body mass index increased were younger than those with no increase (54.7 ± 11.1 versus 59.3 ± 11.2 years; p=0.007). Patients were treated with the following adjuvant chemotherapy regimens: doxorubicin, cyclophosphamide, and paclitaxel (ACT, 129 patients, 65.8%); 5-fluoracil, doxorubicin, and cyclophosphamide (36 patients, 18.4%); cyclophosphamide, methotrexate, and 5-fluoracil (16 patients, 8.2%); docetaxel and cyclophosphamide (7 patients, 3.6%); and other regimen (8 patients, 4.1%). The ACT regimen showed a statistically significant association with increase in the body mass index (p<0.001 by ANOVA). **CONCLUSIONS:** Most patients with breast cancer showed an increase in the body mass index after adjuvant chemotherapy, especially after the ACT chemotherapy regimen.

**Resumo**

**OBJETIVO:** Avaliar variações no índice de massa corpórea em pacientes que estão passando por quimioterapia devido ao câncer de mama, e relacionar tais alterações com a idade da paciente e o regime de quimioterapia. **MÉTODOS:** Estudo de coorte retrospectivo que correlacionou variações no índice de massa corpórea pré- e pós-quimioterapia com a idade da paciente e o regime de quimioterapia. Foram excluídas as pacientes que receberam terapia hormonal prévia, seja como tamoxifen ou inibidores da aromatase. Os dados de 196 pacientes com estágio I a III de câncer de mama foram selecionados, e elas foram tratadas por cirurgia radical ou conservadora que receberam quimioterapia adjuvante no Instituto do Câncer do Estado de São Paulo, Brasil. **RESULTADOS:** Antes da quimioterapia adjuvante, 67,8% das pacientes foram classificadas com sobrepeso ou obesas com base em seus índices de massa corpórea. Aproximadamente 66,3% (IC95% 59,7–73,0) das pacientes exibiram aumento no índice de massa corpórea após a quimioterapia adjuvante. A média de idade das pacientes foi de 56,3 ± 11,3 anos. Pacientes que apresentaram aumento no índice de massa corpórea eram mais jovens do que aquelas que não apresentaram aumento algum (54,7 ± 11,1 versus 59,3 ± 11,2 anos; p=0,007). As pacientes foram tratadas com os seguintes regimes de quimioterapia: doxorubicina, ciclofosfamida e paclitaxel (ACT, 129 pacientes, 65,8%); 5-fluoracil, doxorubicina e ciclofosfamida (36 pacientes, 18,4%); ciclofosfamida, metotrexato e 5-fluoracil (16 pacientes, 8,2%); docetaxel e ciclofosfamida (7 pacientes, 3,6%); e outros regime (8 pacientes, 4,1%). O regime ACT mostrou uma relação significativa com o aumento do índice de massa corpórea (p<0.001 por ANOVA). **CONCLUSÕES:** A maioria das pacientes com câncer de mama mostrou um aumento no índice de massa corpórea pós-quimioterapia adjuvante, especialmente após o regime de quimioterapia ACT.
Introduction

In Brazil, breast cancer is the most common malignant neoplasm for women and one of the ten main causes of death¹. Steroid hormones heavily influence on the disease. Increased estrone and estradiol and reduced sex hormone-binding globulin levels, which result in an increased bio-disposable fraction of estrogen, have been observed in patients with high body mass index (BMI)². As a reference measurement used internationally by the World Health Organization (WHO), BMI is determined by dividing a person's weight by their height squared³.

Chemotherapy (CTx) may be adjuvant or neoadjuvant, depending on whether the cytotoxic agents are administered after or before surgical treatment, respectively. CTx plays an important role in reducing recurrence and improves global survival. However, CTx agents act not only on cancer cells, but also on normal ones, causing some side effects such as nausea, vomiting, loss of appetite, alopecia, mucositis, weakness, fatigue, phlebitis, and myelotoxicity⁴-⁶. Most of these effects have an influence on body weight. Although some women report weight loss, weight gain is more common after CTx⁷-⁹.

Causes of weight gain after CTx have not been fully established, and its etiology seems to be multifactorial. Weight gain occurs because of a positive energy balance and some studies report an increase in the ingestion of calories due to hyperphagia³. Others describe reductions in the energy expended, basal metabolic rate, and physical activity⁹,¹⁰. Another important factor is the combination of glucocorticoids and antiemetics used to minimize the side effects of CTx agents⁸,¹¹. Psychological stress-related emotional volatility and start of menopause may also be related to weight gain during CTx¹². Interruption of ovarian function reduces metabolism, muscle mass, and energy expended, and also stimulates fat accumulation¹³-¹⁵.

In addition to being a risk factor, obesity is related to poorer global survival and specific survival for breast cancer patients¹⁶-¹⁸. Obesity is associated with locally advanced disease at diagnosis and, consequently, a poorer prognosis¹¹,¹⁶,¹⁹. The mechanism has not been well-established, but high BMI values have been usually associated with greater concentrations of circulating sex hormones, insulin, and insulin growth factor, leading to a disequilibrium in the relationship between cell differentiation and apoptosis with a consequent progression and proliferation of tumor cells¹⁶-¹⁸,²⁰.

The purposes of this study were to evaluate variations in the BMI of breast cancer patients undergoing adjuvant CTx, and to relate these changes with the age and CTx regimen employed.

Methods

The goal of this retrospective cohort study was to correlate any variation between pre- and post-CTx BMI with patient’s age and CTx regimen. Out of 221 patients with non-metastatic breast cancer, 196 treated with adjuvant chemotherapy were included in this study. Data were extracted from the electronic records of 196 patients with stage I to III breast cancer who were treated in 2011 at the Cancer Institute of the State of São Paulo (ICESP), in Brazil. The research protocols and the consent process were approved by the Ethics Committee (48/2010). Patients were treated with radical or conservative surgeries and received adjuvant CTx, according to interval protocols. Participants who received any form of prior hormone therapy, such as tamoxifen or aromatase inhibitors, were excluded.

The weight and height of all patients were measured during the first nursing outpatient consultation before the beginning of CTx, using a digital scale (Filizola, Anthropometric Electronic PL 200; 200 kg×50 g). Weight was reevaluated within 30 days after CTx. BMI was calculated as weight (in kg) divided by height (in m²). Patients were classified according to their BMIs, following the guidelines of the National Institutes of Health and the National Heart, Lung, and Blood Institute, as follows: 17≥BMI<18.5, slightly underweight; 18.5≤BMI<25, normal body weight; 25≤BMI<30.0, overweight; 30.02≤BMI≤34.9, grade I obese; 35≤BMI≤39.9, grade II obese; and BMI>40, grade III obese³.

The Kolmogorov-Smirnov test was used to test for the normality of the distribution of continuous variables. Student’s t-test or, when convenient, the Mann-Whitney’s test, was used to compare measurements from two independent groups. The analysis of variance (ANOVA) was used to compare three or more independent groups. Pre- and post-CTx BMI distributions were compared with Student’s t-test for paired measurements. For comparison of these distributions by the type of treatment performed, ANOVA was used. When necessary, sub-hypotheses were tested with Fisher’s Least Significant Difference (LSD) method.

Results

Before starting CTx, 67.8% (n=133) of patients had a BMI≥25. Among them, 40.3% were classified as overweight, 16.8% as grade I obese, 8.7% as grade II obese, and 2.0% as grade III obese. After CTx, 66.3% of the patients (95%Cl 59.7—73.0) had an increase in their BMI. The average (mean±standard deviation) age of all patients was 56.3±11.3 years old. Patients with an increase in their BMI after CTx were younger than those without it (54.7±11.1 versus 59.3±11.1 years old, p=0.007), as seen in Table 1.
There was no difference between the pre-CTx BMIs in the groups of patients with or without a post-CTx increase in the BMI (27.3±5.1 versus 28.3±5.7 kg/m², p=0.2). Among all patients, the average pre- and post-CTx BMIs were 27.7±5.3 and 28.4±5.3 kg/m², respectively, with an average variation of 0.7±2.1 kg/m² (p<0.001). This variation was increased or decreased in the group of patients whose BMI increased or not, respectively, after CTx (for both p<0.001; Table 1).

The following CTx regimens were employed: doxorubicin, cyclophosphamide, and paclitaxel (AC-T, 129 patients, 65.8%); 5-fluoracil, doxorubicin, and cyclophosphamide (FAC, 36 patients, 18.4%); cyclophosphamide, methotrexate, 5-fluoracil (CMF, 16 patients, 8.2%); docetaxel and cyclophosphamide (CT, 7 patients, 3.6%); and other regimens (8 patients, 4.1%), including cycles of paclitaxel and trastuzumab, paclitaxel alone, or docetaxel and cyclophosphamide (AC) (Table 2). Patients who received AC-T were younger (54.2±11 years) than those undergoing other regimens. The AC-T regimen showed an association with the post-CTx BMI change (p<0.001 by ANOVA), as seen in Table 3.
Table 3. Descriptive statistics for pre- and post-chemotherapy body mass indices and comparison between them for each chemotherapy regimen

<table>
<thead>
<tr>
<th>CTx regimen</th>
<th>Evaluation</th>
<th>Mean</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-T</td>
<td>Pre-CTx BMI</td>
<td>27.4</td>
<td>5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Post-CTx BMI</td>
<td>28.3</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>CMF</td>
<td>Pre-CTx BMI</td>
<td>27.6</td>
<td>6.1</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Post-CTx BMI</td>
<td>28.0</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>FAC</td>
<td>Pre-CTx BMI</td>
<td>28.3</td>
<td>5.3</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Post-CTx BMI</td>
<td>29.0</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>Pre-CTx BMI</td>
<td>31.5</td>
<td>5.8</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Post-CTx BMI</td>
<td>30.6</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Pre-CTx BMI</td>
<td>25.8</td>
<td>5.4</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Post-CTx BMI</td>
<td>26.7</td>
<td>6.1</td>
<td></td>
</tr>
</tbody>
</table>

CTx, chemotherapy; SD, standard deviation; AC-T, doxorubicin, cyclophosphamide, and paclitaxel; CMF, cyclophosphamide, methotrexate, 5-fluoracil; FAC, 5-fluoracil, doxorubicin, and cyclophosphamide; CT, docetaxel and cyclophosphamide; BMI, body mass index.

Discussion

Among patients who started adjuvant CTx, 67.8% were overweight. This percentage is slightly higher than the 31% overweight reported in a study including 9,527 patients diagnosed with breast cancer from 1997 to 2007 at participating centers of the National Comprehensive Cancer Network. A Korean study found differences in the BMI between East Asian and Western women. In that study, of the East Asian patients evaluated before CTx, 72.8% were of normal weight, 22.8% were overweight, and 4.3% were obese. Similar data about East Asian women were found in a study including Taiwanese breast cancer patients, which recorded an average pre-CTx BMI of 23.8 kg/m².

Although most patients experienced an increase in their BMI, they remained in the overweight band with BMI values between 25.0 and 29.9 kg/m². Even though many studies have recorded increases in weight and BMI after breast cancer treatment, a systematic review, which included variations in body composition based on the use of imaging exams that quantified adipose tissue and lean body mass, such as densitometry, tomography, and magnetic resonance, did not record a consistent increase in the body weight. Even when there was no weight gain, these patients often had changes to their bodies, with an increase in body fat and reductions in muscle mass and bone density. Two other reviews showed that 50 to 96% of the patients with initial-stage breast cancer gained significant weight during adjuvant treatment, ranging from 2.5 to 6.2 kg. However, weight gains of 10 kg or more were not uncommon.

A criticism of studies that only consider variations in weight is that they do not record the evolution in the body mass composition of skeletal, bone, and adipose tissues during cancer treatment. Body mass does not fully reflect the potentially important changes in lean or adipose tissues. Nonetheless, it is recommended that breast cancer survivors keep their body weights within normal limits during and after treatment.

Considering that CTx-induced ovarian failure occurs in 50 to 70% of women in pre-menopause who receive adjuvant CTx, the post-CTx weight, fat, and lean masses changes essentially mirror those observed in healthy women who undergo natural menopause. In our study, the group of patients who had an increase in their BMIs after CTx was younger than the group with the opposite characteristics. Theoretically, patients with cancer diagnosis who have already experienced changes in their body mass during menopause will have fewer variations throughout cancer treatment. Future studies may want to stratify the women’s menopausal state to analyze changes in the BMI. Population studies in women have demonstrated that specific changes, including an increase in body fat and reduction in lean mass, coincide with aging and are significantly accentuated from the start of natural menopause, with higher rates of increased weight in the initial post-menopausal years.

Anthracycline-based CTx regimens were associated with the greatest rise in BMI, with a statistically significant value for the AC-T regimen and a near-significant one for the FAC regimen. The CMF and CT regimens were not statistically related to an increase in the BMI. Changes in BMI during anthracycline-based CTx have been associated with poorer prognosis, in terms of increased recurrence and mortality rates. However, other studies have recorded only slight weight gains or unchanged weight with anthracycline-based regimens.

One limitation of our study is the small number of patients who received the CMF regimen. Other investigations with more participants have shown that such regimen, or those based on cyclophosphamide, were related to higher rates of weight gain. One mechanism responsible for this increased weight gain is the higher dose of cyclophosphamide, which is an alkalizing agent that induces amenorrhea and menopause more often than anthracyclines.

In addition to adjuvant therapy, be it CTx, hormone therapy, or immunotherapy with trastuzumab-type monoclonal antibodies, metabolic and endocrine factors related to an increase in weight gain after cancer diagnosis are strongly associated with higher risk of recurrence and reduction in survival rates.

Advances in the clinical management of breast cancer, including early detection, new CTx regimens, and targeted treatments with anti-estrogens or trastuzumab,
have improved survival rates for women with breast cancer. However, weight gain and unfavorable changes in body composition, particularly central adiposity, after treatment, can increase morbidity and mortality due to other chronic degenerative diseases, such as diabetes, cardiovascular disease, and colon cancer. There is a need for campaigns targeted towards this group of women, and for institutional programs focused on helping patients maintain their BMIs within normal standards during and after CTx.

Most patients with breast cancer showed an increase in BMI after adjuvant CTx. This change was mostly associated with the AC-T CTx regimen. In future studies to identify the start of chemotherapy, menopausal state may relate to the role of adjuvant therapy on weight gain, or hormonal changes in menopause.

References


