Estrone and Estradiol Levels in Breast Cancer Patients Using Anastrozole Are Not Related to Body Mass Index

Níveis de estrona e estradiol em pacientes com câncer de mama usando anastrozol não estão relacionados ao índice de massa corpórea

Eduardo Borges Coscia[1] Maricene Sabha[1] Marli Gerenutti[1] Francisco Carlos Groppo[2] Cristiane de Cássia Bergamaschi[1]

[1] Department of Pharmaceutical Sciences, Universidade de Sorocaba, Sorocaba, São Paulo, Brazil
[2] Department of Pharmacology, Anesthesiology and Therapeutics, Faculdade de Odontologia de Piracicaba, Universidade Estadual de Campinas, Piracicaba, Brazil

Address for correspondence Cristiane de Cássia Bergamaschi, Department of Pharmaceutical Sciences, Universidade de Sorocaba – UNISO, Rodovia Raposo Tavares, Km 92.5, 10023-000, Sorocaba, SP, Brazil (e-mail: cristiane.motta@prof.uniso.br).

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Abstract

Objective Obesity is associated with an increased risk for breast cancer. Recent studies have shown that aromatase inhibitors may be less effective in women with a high body mass index (BMI). The aim of this study was to establish the relationship between the BMI and plasma estrone and estradiol levels in postmenopausal women with hormone receptor-positive breast cancer using anastrozole.

Methods In this cohort study, the patients were divided into three groups according to BMI (normal weight, overweight and obese) to compare and correlate plasma hormone levels before starting anastrozole hormone therapy and three months after treatment. Plasma hormone levels were compared for age and use of chemotherapy.

Results A statistically significant reduction in estrone and estradiol levels was observed between baseline and three months after starting the anastrozole treatment ($p < 0.05$). There was no statistically significant difference in plasma estrone and estradiol levels among the BMI groups ($p > 0.05$), but a significant reduction in plasma estrone levels was observed after three-months' treatment relative to baseline in all groups, as well as a reduction in estradiol in the obese group ($p < 0.05$). The use of chemotherapy and age > 65 years had no influence on plasma steroid levels.

Conclusion Changes in estrone and estradiol levels in the studied groups were not associated with BMI, chemotherapy or age.

Keywords
- breast neoplasms
- estrone
- estradiol
- body mass index
- anastrozole

Resumo

Objetivo A obesidade está associada com risco aumentado de câncer de mama. Estudos recentes têm mostrado que os inibidores de aromatase podem ser menos eficazes em mulheres com alto índice de massa corporal (IMC). O objetivo deste estudo foi estabelecer a relação entre o IMC e os níveis plasmáticos de estrona e estradiol em

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mulheres no período pós-menopausa com câncer de mama receptor hormonal positivo, em tratamento com anastrozol.

Métodos Este estudo de coorte acompanhou três grupos de pacientes de acordo com o seu IMC (peso normal, sobrepeso e obesidade), a fim de comparar e correlacionar as dosagens dos hormônios estrona e estradiol antes e após três meses do uso do anastrozol. Os níveis plasmáticos dos hormônios foram também relacionados à idade do paciente e ao uso da quimioterapia.

Resultados Redução estatisticamente significativa de estrona e estradiol foi observada entre os níveis basais e três meses após o início do tratamento com anastrozol ($p < 0,05$). Não houve diferença estatisticamente significativa entre os níveis plasmáticos de estrona e estradiol em relação ao IMC ($p > 0,05$), mas houve redução significativa entre os níveis plasmáticos basais de estrona após o tratamento em todos os grupos, e redução de estradiol no grupo de pacientes obesas ($p < 0,05$). A condução da quimioterapia e da idade acima de 65 anos não interfere com os níveis plasmáticos de esteroides.

Conclusão Os níveis plasmáticos de estrona e estradiol nos grupos estudados não foram alterados em termos de IMC, quimioterapia e idade.

Palavras-chave
- neoplasias de mama
- estrona
- estradiol
- índice de massa corporal
- anastrozol

Introduction

Breast cancer is the neoplasm that causes the highest number of deaths among Brazilian women. The estimates for the year 2014 in Brazil were around 57,120 new cases, according to data from the Brazilian National Cancer Institute.[1] The disease is also considered a public health problem in the United States, where the estimate for 2012 was of 229,060 new cases and 39,920 deaths.[2]

Older age is the biggest risk factor for breast cancer, and other risk factors are also well established, including early menarche, nulliparity, prolonged use of oral contraceptives, late menopause, menopausal hormone therapy for over five years, family history of breast cancer, and high density of breast tissue.[1]

Serum estrogen and androgen levels in postmenopausal women also affect the risk of breast cancer. An elevated plasma estrone level is strongly associated with the risk of developing the disease, and in women with estradiol or testosterone levels 20–25% above the mean values, the incidence of breast cancer is 2 to 3 times higher.[3]

Besides the above-mentioned factors, Cintra et al[4] and Friedenreich[5] reported that obesity is correlated with a 30–50% higher relative risk of breast cancer in menopausal women, and that this population has a greater risk of death and recurrence.[6,7] According to Colditz et al[8] and Suzuki et al[9], there is a positive association between high body mass index (BMI) and breast cancer risk in post-menopausal patients with hormone receptor-positive tumors.

Approximately 78% of breast tumors are hormone dependent. Therefore, stopping the action of estrogen in the breast is a known therapeutic approach for preventing recurrence, and it can be achieved by blocking the hormone's action on the estrogen receptors or stopping its synthesis.[10]

During a woman's period of menstrual activity, estrogens are synthesized mainly by the ovaries. In the postmenopausal phase, the suprarenal cortex and the ovaries produce androgens, which are then converted into estrogens by the aromatase enzyme, an enzyme complex that is part of the cytochrome P-450 family and is present mainly in the adipose tissue, striated muscles, the liver, and breast tumors.[11]

According to Diorio et al[10], an elevated BMI is associated with higher estrogen levels in postmenopausal women due to the fact that the adipose tissue is the main site for the synthesis of these steroids. These increased estrogen levels may play a role in the development of breast tumors.

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Aromatase inhibitors belong to a group of drugs widely used for breast cancer hormone therapy, whose aim is to decrease estrogen levels and deactivate the aromatase complex, in order to stop the conversion of androstenedione into estrone, and of testosterone into estradiol. Anastrozole is the best-known example from this group of drugs.[12]

Anastrozole's action is exerted through a competitive link with the aromatase enzyme, and it decreases estrogen biosynthesis in all tissues. In menopausal women with breast cancer, anastrozole at 1mg/day inhibits aromatization by 96.7%, and suppresses plasma estrone and estradiol concentrations by $\sim$ 84–94%.[13]

According to Sestak et al[14], aromatase inhibitors seem to be more effective in leaner menopausal women. There are data demonstrating an increased risk of breast cancer recurrence, and of death after recurrence, among women who have elevated BMIs undergoing hormone therapy

with anastrozole compared with patients treated with tamoxifen.[15] A possible explanation for this relationship is that women with elevated BMIs have higher estrogen levels due to the incomplete inhibition of the peripheral aromatization by anastrozole.[14]

Studies such as that by Goodwin and Pritchard[15] examine whether patients with elevated BMIs need higher doses of aromatase inhibitors in order to reach therapeutic levels of estrogen suppression. The present study sought to evaluate estrone and estradiol suppression by anastrozole in postmenopausal patients with hormone receptor-positive breast cancers, and its relationship with BMI values.

Methods

Study Design

Cohort study.

Patients

Patients diagnosed with breast cancer, in the postmenopausal phase, and oncologically indicated for adjuvant hormone therapy with anastrozole were selected to participate in the study during the period of hormone therapy prescription. All participants had natural menopause and had not been submitted to hormone treatment during this phase. The patients were drawn from four centers specialized in oncology and breast cancer treatment located in the city of Sorocaba, in the state of São Paulo, Brazil.

Eligibility Criteria

Patients diagnosed with: hormone receptor expression for estrogen and progesterone in breast cancer; post-menopause status characterized by amenorrhea for over a year before the beginning of the oncological treatment; and indicated for anastrozole hormone therapy were included.

Patients were excluded for the following: previous treatment with tamoxifen; contraindication for the use of anastrozole; previous hysterectomy or oophorectomy; the use of menopausal hormone therapy during the study period; corticosteroid treatment during the study period; mental deficits that could affect the understanding of study; individuals that interrupted treatment due to personal reasons or oncological indication; disease recurrence during study period; and those unable to use anastrozole during study period.

Clinical Protocol

The initial care of each patient was conducted at the time of the beginning of the anastrozole treatment. All participants had medical prescriptions and access to the medication, which was provided by pharmacies within the city's oncological center. Appointments were scheduled in the morning period between 7am and 8am, so that patients could follow an eight-hour fasting.

The clinical protocol for the first appointment included: an interview and an analysis of the medical charts in order to obtain the clinical and epidemiological data; BMI measurement (kg/m^2) according to the World Health Organization (WHO); blood collection; and orientation on the use of anastrozole regarding posology (single oral dose of 1mg/day), and on the importance of adhering to the treatment and recording the possible adverse effects related to the medication. The patients were asked to keep the empty medication boxes and blisters so that they could be checked on the second appointment.

The second appointment was conducted 90 ± 7 days after the first appointment. The patients were resubmitted to an interview and an analysis of the medical charts in order to complement the clinical information, reevaluate the anthropometric data and collect a new blood sample for the determination of plasma steroid levels.

In order to evaluate the relationship between the BMI and the suppression of estrone and estradiol by anastrozole, patients were divided into three groups: 1) normal weight patients (BMI < 25.00 kg/m^2); 2) overweight patients (BMI of 25.00–29.99 kg/m^2); and obese patients (BMI > 30.00 kg/m^2). The influence of age (< 65 and ≥ 65 years old) and chemotherapy use (yes/no) on the plasma levels of these steroids was also investigated.

The adherence to the anastrozole treatment was checked by verifying the records from the high-cost medicine pharmacy where the drugs were dispensed. Adherence was also checked by telephone contact with the patient 60 days after the start of treatment, and confirmation was made during the second appointment by checking the empty blisters from the boxes of anastrozole used.

Blood Sample Collection

Blood samples (5 ml for each hormone) were centrifuged at 2,200 g for 10 minutes at a temperature of 18°C, and the serum frozen at -20°C. Plasma estrone levels (pg/mL) were measured by radioimmunoassay and estradiol (pg/mL) by the competitive electrochemiluminescence-based immunoassay method. Values were considered within the normal range for menopause patients when the following were observed: estrone $\leq$103 pg/mL and estradiol $\leq$ 55 pg/mL. The lower limits of detection for the methodologies employed were 10 pg/mL and 5 pg/mL respectively.

Statistical Analysis

Non-parametric tests, including the Kruskal-Wallis, Mann-Whitney, Wilcoxon, Chi-square ($\chi 2$), and the parametric Student's *t*-test were used. Pearson's correlation coefficient was employed to analyze the correlation between variables. The statistical software used was Bioestat 5.0 (Instituto Mamirauá, Tefé, Brazil), with a significance level of 5%.

Ethical Aspects

This study was approved by the Research Ethics Committee of Universidade de Sorocaba (protocol number 021/11). After having understood the study, the patients formalized their participation by signing the Free Informed Consent Form.

Results

The 38 eligible patients completed the study. The mean age was 64.94 ± 9.40 years, and 11 patients were of normal weight, while 9 were overweight and 18 were obese. No patients had their BMIs reclassified on the reevaluation of the anthropometric indexes (►**Table 1**).

Table 1 Clinical variables of breast cancer patients treated with anastrozole

Variable	Normal weight ($n = 11$)	Overweight ($n = 9$)	Obese ($n = 18$)	Total ($n = 38$)
BMI (kg/m^2) Mean ± SD	23.8 ± 0.99	27.57 ± 1.03	34.0 ± 3.09	29.51 ± 5.01
Age (years)				
48–64	4	4	10	18 (47.40%)
65–85	7	5	8	20 (52.60%)
Mean ± SD	66.5 ± 10.93	67.14 ± 12.40	63.0 ± 6.65	64.94 ± 9.40
TM (years)				
1–10	4	3	6	13 (34.10%)
> 10	7	6	12	25 (65.90%)
AM (years old)				
41–50	5	4	11	20 (52.60%)
51–55	6	5	7	18 (47.40%)
Stage				
I	4	2	6	12 (31.60%)
II A	2	4	5	11 (28.90%)
II B	4	3	4	11 (28.90%)
III A	1	0	2	3 (7.90%)
III C	0	0	1	1 (2.70%)
Chemotherapy				
No	4	3	6	13 (34.20%)
Yes	7	6	12	25 (65.80%)
Total	11	9	18	38 (100%)

Abbreviations: AM, age at menopause; BMI, body mass index; TM, time at menopause; SD, standard deviation.

Among the possible adverse effects related to anastrozole, 31.6% (n = 12) reported some discomfort; 13.2% ($n = 5$), muscle pains; 10.5% ($n = 4$), joint pains; and 7.9% ($n = 3$) reported hot flashes. All patients confirmed taking anastrozole daily; they delivered the empty blisters at the second appointment, and obtained the medicine during the period of use, which was confirmed by checking the records at the high-cost drug pharmacies.

A statistically significant reduction was found between measurements at baseline and after three months of treatment for both hormones (Student's *t*-test, $p = 0.0001$) (►**Table 2**). The reductions averaged 48.8% for estrone and 39.9% for estradiol.

►**Fig. 1** shows plasma estrone and estradiol levels at baseline and three months after starting treatment with anastrozole according to BMI, age and chemotherapy use. No difference was observed among the groups (Kruskal-Wallis test, $p \geq 0.05$) for any of the hormones studied in relation to the BMI. There was a reduction (Wilcoxon test, $p < 0.005$) in plasma estrone concentration after treatment with

Table 2 Plasma estrone and estradiol levels (pg/mL) of menopausal women with breast cancer, before and after treatment with anastrozole

Measurements	Estrone		Estradiol	
	Baseline (pg/mL)	Post-treatment (pg/mL)	Baseline (pg/mL)	Post-treatment (pg/mL)
Mean ± SD	26.63 ± 5.82*	13.63 ± 4.51*	10.08 ± 7.70#	6.05 ± 2.81#
Median	22	12	7	5
Minimum and maximum	10–79	10–25	5–41	5–16
1st and 3rd quartiles	15–28	10–15	5–13	5–5

Abbreviation: SD, standard deviation.
Note: *#Statistically significant difference (Student's *t*-test, $p = 0.0001$) between measurements at baseline and post-treatment.

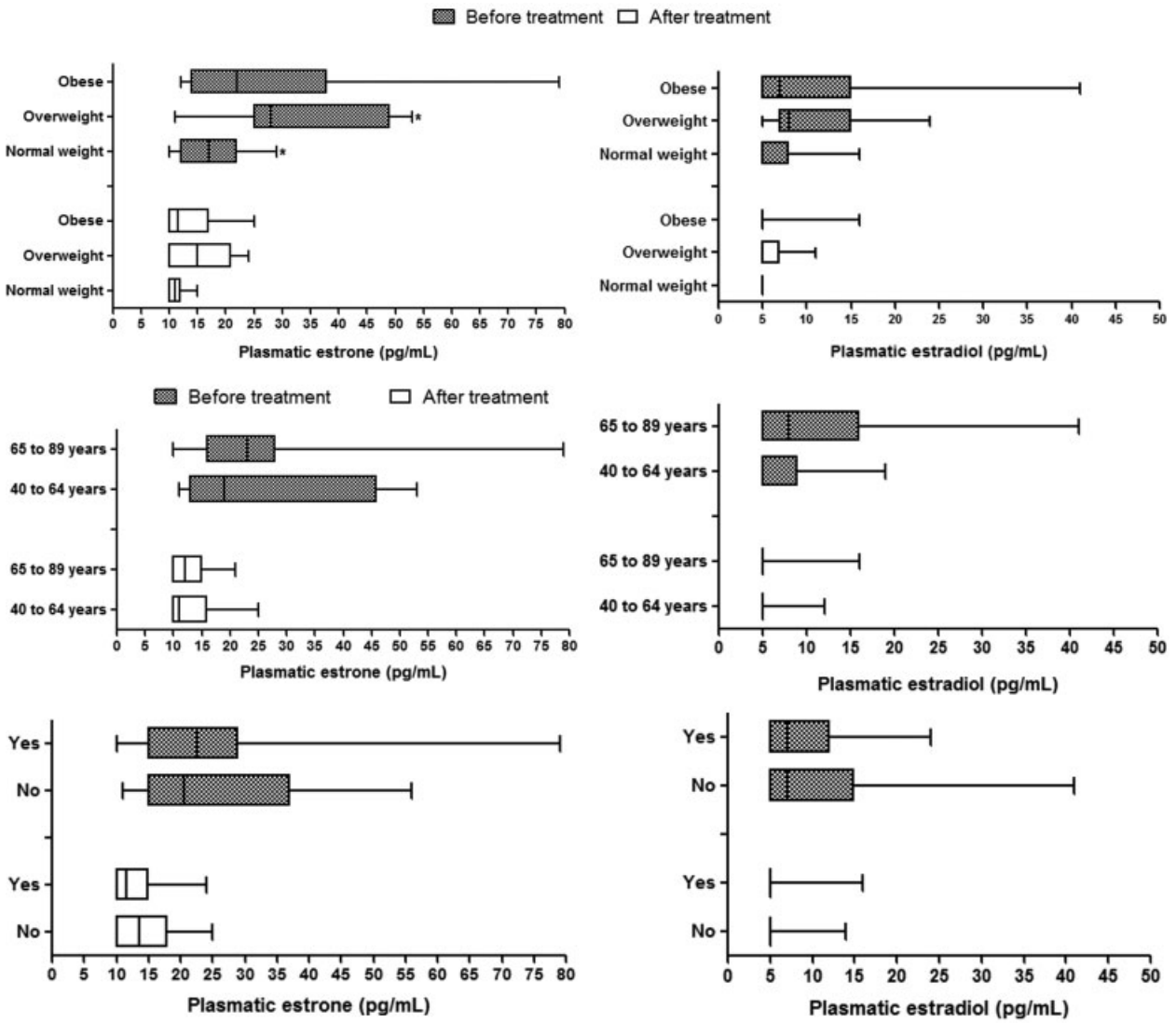

Fig. 1 Plasma estrone and estradiol concentrations – median, [first] and [third] quartiles, maximum and minimum (pg/mL) values before and three months after treatment with anastrozole, according to * body mass index (#), age (##) and chemotherapy use (###). *A statistically significant difference was observed in the intergroup comparison (Kruskal-Wallis test, $p < 0.05$) in the normal weight and overweight groups for plasma estrone values at baseline. #No difference was found on the intergroup comparison (Kruskal-Wallis test, $p \geq 0.05$) for hormone concentrations. A statistically significant difference was observed in the intergroup comparison (Wilcoxon test, $p < 0.05$) for estrone, and in the obese group, for estradiol. ##No statistically significant difference was found on the intergroup comparison (Mann-Whitney test, $p \geq 0.05$). A statistically significant difference was found on the intergroup comparison (Wilcoxon test, $p < 0.001$) for estrone, and in the 65–89 year-old group, for estradiol. ###No statistically significant difference was found on the intergroup comparison (Mann-Whitney test, $p \geq 0.05$). A statistically significant difference was found on the intergroup comparison (Wilcoxon test, $p < 0.05$).

anastrozole in the three groups evaluated, and a reduction in plasma estradiol levels only for the obese group (Wilcoxon test, $p = 0.0009$). The correlation between BMI values and plasma hormone concentrations after treatment with anastrozole was weak and non-significant ($p \geq 0.05$).

No difference was found for the estradiol and estrone groups (Mann-Whitney test, $p \geq 0.05$) in relation to age. However, a significant reduction in plasma estrone levels (Wilcoxon test, $p < 0.001$) was found for both groups, whereas a reduction in plasma estradiol levels was detected only for the group of patients aged > 65 years (Wilcoxon test, $p = 0.007$). The correlation between age and plasma hormone concentrations after the anastrozole treatment was weak and non-significant ($p \geq 0.05$).

There was no statistically significant difference among hormone levels in the group of patients submitted to chemotherapy treatment (Mann-Whitney test, $p \geq 0.05$). A significant reduction in plasma hormone concentrations was observed for both groups after the anastrozole treatment (Wilcoxon test, $p < 0.05$).

Discussion

The use of anastrozole led to a statistically significant reduction in plasma estrone and estradiol levels. However, no

significant changes in steroid concentrations were associated with BMI group. This result contradicts the hypothesis of the study that there would be a smaller reduction in these hormone levels among obese patients. No influence of age or use of chemotherapy (or otherwise) on the plasma levels of these steroids was observed.

The group of patients included in this study comprised predominantly older women, an expected characteristic due to the fact that age is a risk factor for breast cancer. The association between an elevated BMI and breast cancer risk applies mainly to postmenopausal women,[2,6,7] where obese women have a 2.5 times greater chance of developing breast cancer than those with a normal BMI.[16]

Approximately 78% of breast neoplasms are hormone dependent in postmenopausal women, characterized by the expression of estrogen and progesterone receptors.[10] All patients involved in this study tested positive on immunohistochemistry exams for the expression of receptors, a fundamental criteria for the indication of hormone therapy, which is considered a safe and effective treatment for breast cancer.[17]

The decision to use anastrozole as the hormone therapy for the patients involved in the research was based on the characteristics of the population, which was composed of women in the postmenopausal phase with breast cancer. During this phase, treatment with aromatase inhibitors is associated with higher disease-free survival rates than therapy with tamoxifen.[18,19]

In menopausal women with breast cancer, anastrozole at a dose of 1 mg/day inhibits aromatization by $\sim$ 97% and suppresses plasma estrone and estradiol concentrations by $\sim$ 84% and 94% respectively.[13] The time required for anastrozole to promote estrogen suppression is two to four days.[20,21] After approximately 7 days of administration, anastrozole reaches 90 to 95% of its plasma concentrations. In the present study, the patients were reevaluated three months after the beginning of the treatment, which is in accordance with the studies of Dixon et al,[22] Smith et al,[23] and Folkerd et al.[6]

This time period allowed the collection of other information regarding the adverse effects possibly attributed to anastrozole, as well as information on the adherence to the treatment and on the occurrence of oncological events that patients with neoplasms are exposed to, such as treatment complications and the possibility of the loco-regional or distal recurrence of the disease.

Despite the benefits of hormone therapy with aromatase inhibitors, recent reports suggest decreased efficacy, increased rates of recurrence, and of death after recurrence, with the use of anastrozole in obese postmenopausal breast cancer patients compared with women of normal weight undergoing treatment with anastrozole and with obese women treated with tamoxifen.[6,14,15]

Folkerd et al[6] confirmed a positive relationship between estrogen levels and BMI during treatment with anastrozole; that is, a higher BMI was associated with higher plasma steroid concentrations. This result may help explain the lower benefit observed when treating obese women with anastrozole, where breast cancer is associated, among other factors, with circulating estrogen levels.[23–25]

Diorio et al[10] reported results similar to those of the present study. The authors compared estradiol levels between lean and obese women treated with aromatase inhibitors (letrozole, exemestane or anastrozole) and found that, although postmenopausal obese women had higher levels of the hormone, the aromatase inhibitor therapy appeared to be equally effective in decreasing the levels of this steroid, irrespective of the BMI. More recently, Lønning et al[26] also found no correlation between estrogen levels and BMI in breast cancer patients treated with letrozole or anastrozole.

Thus, the impact of obesity on the risk of breast cancer recurrence[27] may not be due to the complete inhibition of the peripheral conversion of androgens without estrogens by aromatase in patients treated with anastrozole. To date, scant studies analyzing female sex hormones according to BMI, as investigated in the present study, have been conducted.

Body mass index is the most used anthropometric parameter in scientific studies for characterizing the overweightness or obesity of an individual.[14–28] Although the BMI is an index based on height and weight that precludes specific evaluation of lean mass and fat mass, major muscle gain in a group of menopausal women is improbable. Therefore, an increased BMI can be attributed to increased body fat.[29]

Body fat percentage is also an anthropometric index predicting risk. However, this evaluation in large-scale studies is subject to technical and inter-observational variations, because it is not as easily calculated as height and weight, which explains why most published studies use BMI calculation as a parameter to associate obesity and cancer.[21,30,31]

The results of the present study showed the adherence of the group to the prescribed treatment. According to Murphy et al[32], in order to be considered adherent to treatment, patients must exhibit evidence of the use of medication above 80% for a given period of time.

Danilak and Chambers[33] reported 78% adherence to hormone therapy for breast cancer, which was retrospectively confirmed by records held by the registered pharmacies where the drugs were dispensed. This methodology was also used in the present study, together with individual confirmation of medication use by patients and the checking of the empty anastrozole blisters. This adherence was of 100%, which is justified by the short observation period (three), unlike the cited studies, which had a longer evaluation period, of at least two years.

The adverse effects likely attributable to the use of anastrozole in this study were similar to those found in the literature,[18,21] in which the most frequent complaints were of muscle pains, hot flashes, and joint pains, mirroring those described by the Food and Drug Administration (FDA).

It was not possible to quantify plasma steroid levels below 10 pg/mL for estrone, and below 5 pg/mL for estradiol. The ability to determine plasma steroid levels below this limit might have resulted in a greater percentage reduction in these hormones.

In the literature, there are few studies evaluating the relationship between BMI and the decreased efficacy of aromatase inhibitors, and the available results remain conflicting. The results of the present study showed that changes in plasma estrone and estradiol levels in the group studied were not associated with BMI, chemotherapy or age.

Conflict of Interest

The authors have no potential conflict of interest to declare.

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