

Genitourinary symptoms and quality of life of women with breast cancer undergoing chemotherapy

Sintomas geniturinários e qualidade de vida de mulheres com câncer de mama em tratamento quimioterápico

Síntomas geniturinarios y calidad de vida de mujeres con cáncer de mama en quimioterapia

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ABSTRACT | This study aimed to compare genitourinary symptoms and quality of life in women with breast cancer before and after chemotherapy treatment. This is a prospective and analytical study carried out with 60 women treated at a hospital in the state of Paraná. Sociodemographic data, menopausal status, climacteric symptoms, quality of life, and pelvic floor strength and resistance were collected. Descriptive statistics, t-tests, Shapiro-Wilk, Cochran, Factorial Analysis of Variance for Repeated Measures and Fishers least significance difference were used for data analysis. Participants suffered genitourinary alterations, such as reduced strength and resistance of the pelvic floor muscles, urinary incontinence and vulvovaginal atrophy, regardless of the evaluated factors (type of chemotherapy, parity, and menopausal status). Therefore, greater attention and discussion by multidisciplinary health teams is necessary, as these symptoms can be reduced and managed if recognized early.

Keywords | Lower Urinary Tract Symptoms; Quality of Life; Breast Neoplasms; Women's Health; Drug-Related Side Effects and Adverse Reactions.

RESUMO | Este estudo teve como objetivo comparar os sintomas geniturinários e a qualidade de vida de mulheres com câncer de mama antes e após o tratamento quimioterápico. Trata-se de um estudo prospectivo e analítico realizado com 60 mulheres atendidas em um

hospital no estado do Paraná. Foram coletados dados sociodemográficos, status menopausal, sintomas do climatério, qualidade de vida e força e resistência do assoalho pélvico. Utilizou-se estatística descritiva, assim como os testes t, de Shapiro-Wilk, de Cochran, análise da variância fatorial para medidas repetidas e método LSD de Fisher para análise dos dados. As participantes sofreram alterações geniturinárias como redução de força e resistência dos músculos do assoalho pélvico, incontinência urinária e atrofia vulvovaginal independente dos fatores avaliados (tipo de quimioterapia, paridade e status menopausal). Entende-se que é necessário que haja maior atenção e discussão por parte das equipes multiprofissionais de saúde, pois esses sintomas, se reconhecidos precocemente, podem ser reduzidos e gerenciados.

Descritores | Sintomas do Trato Urinário Inferior; Qualidade de Vida; Câncer de Mama; Saúde da Mulher; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos.

RESUMEN | Este estudio tuvo como objetivo comparar los síntomas geniturinarios y la calidad de vida en mujeres con cáncer de mama antes y después del tratamiento con quimioterapia. Se trata de un estudio prospectivo y analítico realizado con 60 mujeres que recibieron atención en un hospital del estado de Paraná (Brasil). Se recogieron datos sociodemográficos, estado menopáusico, síntomas

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climatéricos, calidad de vida y fuerza y resistencia del suelo pélvico. Se utilizaron estadísticas descriptivas, pruebas t de Shapiro-Wilk y de Cochran, análisis factorial de varianza para medidas repetidas y LSD-Fisher para el análisis de datos. Las participantes sufrieron alteraciones genitourinarias, como disminución de la fuerza y resistencia de los músculos del suelo pélvico, incontinencia urinaria y atrofia vulvovaginal, independientemente de los factores evaluados

(tipo de quimioterapia, paridad y estado menopáusico). Se concluye que es necesaria una mayor atención y discusión por parte de los equipos de salud multidisciplinares, ya que estos síntomas pueden reducirse y manejarse si se reconocen a tiempo.

Palabras clave | Síntomas del Sistema Urinario Inferior; Calidad de Vida; Neoplasias de la Mama; Salud de la Mujer; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos.

INTRODUCTION

Breast cancer is the most common neoplasm in women worldwide¹. Despite the high incidence, the evolution of the forms of diagnosis and treatment has been promoting the decline of mortality rates, resulting in a significant increase in long-term survival, which arouses researchers' interest in understanding the adverse events caused by the treatments and their influence on the quality of life (QoL) of this population^{2,3}.

Genitourinary symptoms, such as urinary incontinence (UI) and vulvovaginal atrophy, are some of these adverse events and are related to ovarian dysfunction and the reduction of estrogen⁴. Its prolonged deficit can lead to atrophy of the vulva, vagina, lower urinary tract and supporting pelvic structures, which can cause urinary dysfunctions, discomfort/pain, impaired sexual function, and negative impact on several domains of QoL⁴.

Furthermore, genitourinary syndrome is more prevalent in women with breast cancer, and may have an early onset due to treatments, if not diagnosed and treated in a timely and appropriate manner⁵. A systematic review with meta-analysis showed a higher prevalence of UI among women with breast cancer (38%) than among those without the disease (21%)⁶. The significant association between UI and lower sexual satisfaction scores should also be considered⁷.

Despite this, little is discussed about the diagnosis of genitourinary symptoms and the impact on QoL resulting from ovarian dysfunction caused by chemotherapy treatment in women with breast cancer.

Objective

To compare the occurrence of genitourinary symptoms and the QoL of women with breast cancer before and after chemotherapy treatment.

METHODOLOGY

Study design, location, and period

This prospective, analytical, and quantitative study considered the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) framework for its elaboration. Data collection was performed at the mastology outpatient clinic of a hospital located in the west of the state of Paraná, Brazil, from August 2017 to December 2018.

Population and sample: inclusion and exclusion criteria

A sample size calculation was performed assuming an F-distribution for the application of the analysis of variance (ANOVA) for repeated measures with two dependent measures, and as parameters a 0.05 type I error, a 0.25 mean effect size and a 0.90 power analysis were used. The equivalent of n=60 women was obtained using the G*Power program.

Thus, 60 women were included, respecting the following inclusion criteria: women diagnosed with breast cancer; up to 60 years of age; after breast surgery; and who were starting chemotherapy treatment with cyclophosphamide for the first time. The exclusion criteria adopted were: women with impaired reading and comprehension; who presented metastasis or new malignant tumor; who had already received chemotherapy treatment for breast cancer or another type of cancer; with neurological disorders associated with mobility (paraplegia, previous stroke with hemiplegia, multiple sclerosis, severe rheumatoid arthritis, or musculoskeletal disorders), severe uterine prolapses and vaginal dystopias; previously subjected to perineal surgeries; and pregnant or postpartum women.

Women who met the inclusion criteria of the research were invited to participate in the days of care at the outpatient clinic. Interviews and research procedures were conducted in the room previously reserved for this purpose.

Study protocol

Data collection was performed in two moments: before (T0) and 30 days after the end of adjuvant chemotherapy treatment (T1). The instruments and questionnaires used are described below:

Sociodemographic and medical questionnaire: collects data regarding age; schooling level; marital status and self-reported race; previous comorbidities; obstetric history; histological type of cancer; clinical staging; presence of estrogen or progesterone hormone receptors; type of surgery received. These data were obtained in an interview with the participant and by a medical record review collected at T0.

Menopausal status: classifies menopausal status according to the Breast Cancer Surveillance Consortium (BCSC) into premenopause, perimenopause, postmenopause, and surgical menopause/others⁸. This classification was applied at T0 and T1.

Menopause rating scale (MRS): quantifies the intensity of symptoms presented by climacteric women and consists of 11 items distributed in three domains: (1) somatic-vegetative—shortness of breath, sweating, hot flashes, heart malaise, sleep problems, and muscle and joint problems (items 1–3 and 11, respectively); (2) psychological—depressive mood, irritability, anxiety, and physical and mental exhaustion (items 4–7, respectively); and (3) urogenital—sexual, bladder and vaginal dryness problems (items 8–10, respectively). Each item can be graded from 0 to 4 (0=no symptoms; 1=little severe; 2=moderate; 3=severe; and 4=very severe). The total score of the scale results from the sum of the scores of the three subscales, and the symptoms are classified as: asymptomatic or scarce (0–4 points), mild (5–8 points), moderate (9–15 points), or severe (more than 16 points)⁹. This scale was applied at T0 and T1.

International consultation on incontinence questionnaire – short form (ICIQ-SF): evaluates how often urine leaks (question 3), how urine leaks (question 4), the impact of UI on daily life (question 5) and when urine leaks (question 6). The total score of the ICIQ-SF results from the sum of the values scored in questions 3, 4, and 5,

ranging from 0 to 21 points; and the higher the score, the greater the severity and impact of UI on QoL¹⁰. This scale was applied at T0 and T1.

Perineometry: evaluates the contraction pressure exerted by the pelvic floor muscles (PFMs) using the perineometer device of the brand Perina® (QUARK medical products, Brazil). Notably, the perineometer indirectly evaluates the contraction strength. For the evaluation, the woman was placed in a modified lithotomy position and bidigital palpation was performed for identifying the PFMs with the hand properly gloved and greased in gel, avoiding gluteal, abdominal, or anal contraction^{11,12}. After verifying the understanding of the PFMs contraction by bidigital palpation, a latex vaginal pressure probe was introduced, deflated, coated with a latex condom, using a water-based lubricant gel, so that only 0.5 to 1 cm of the device was visible¹³. The probe was slowly inflated until the woman felt a slight pressure on the vaginal wall, and then the pressure was set to ± 1 ¹². For the strength evaluation, three voluntary contractions with maximum strength of the PFMs were requested, with 10 second intervals, recorded in centimeters of water (cmH₂O)¹². Then, for the resistance test, three sustained and interval contractions were requested, verifying the maximum times, with one-minute intervals¹⁴. For data analysis, the observed average values of maximum peak force, also called rapid contraction, and the time of the sustained PFMs contraction, slow contraction¹⁴, were considered. This evaluation was applied at T0 and T1.

Analysis of results and statistics

Descriptive statistics were used to evaluate the association between the variables related to the characterization of the interviewees (sociodemographic, medical, and reproductive profile).

MRS, ICIQ-SF, and perineometry data at T0 and T1 were evaluated using the Shapiro-Wilk and Cochran tests, considering menopausal status and number of childbirths as explanatory variables. Once the data were in accordance with these assumptions, the factorial analysis of variance (ANOVA) for repeated measures and Fisher least square difference (LSD) method were applied. Regarding when UI occurs, the frequencies of responses to question 6 of the ICIQ-SF, at T0 and T1, were evaluated and compared between the two periods by the chi-square test for independence. The statistical program STATISTICA 7.0 was used.

The matrices of the perineometry, MRS and ICIQ-SF variables were standardized and analyzed by principal component analysis (PCA). The factor loadings resulting from the principal components were evaluated regarding the type of chemotherapy, the period of treatment, the menopausal status, and the number of childbirths. The evaluations performed by type of chemotherapy and number of childbirths were performed with one-way ANOVA, followed by the Tukey's honestly significant difference.

The evaluation regarding the treatment period was performed with the Student's *t*-test for dependent samples, while the evaluation regarding the menopausal status was performed with the *t*-test for independent samples. A 0.05 significance level was used in these tests, which were performed with the R programming language.

Ethical aspects

The study was conducted in accordance with the principles of the Declaration of Helsinki and under the Resolution No. 466/2012 of the National Health Council, linked to the Brazilian Ministry of Health. It should be noted that, at the end of the study, women who presented urogenital alterations were referred to the Physical Therapy outpatient clinic of the study hospital or to other specialized services, according to the participant's need.

RESULTS

Table 1 describes the data of the sociodemographic profile and breast cancer of the sample (n=60).

Table 1. Characterization of sociodemographic and medical variables of women with breast cancer undergoing chemotherapy, Paraná, Brazil, 2017-2018

Characteristic	n=60	%
Age	46.3 (SD±5.77)	
Skin color		
White	47	78.3
Mixed-race	9	15
Black	3	5
Yellow	1	1.7
Schooling level		
≤8 years	37	61.7
>8 years	23	38.3

(continues)

Table 1. Continuation

Characteristic	n=60	%
Marital status		
With a partner	51	85
Without a partner	9	15
Comorbidities*		
Chronic arterial hypertension	21	35
Diabetes mellitus	4	6.7
Others	10	16.7
Clinical staging		
I	18	30
IIA	24	40
IIB	10	16.7
IIIA	6	10
IIIB	2	3.3
Estrogen receptor +	40	66.7
Progesterone receptor +	38	63.3
HER2-	40	66.7
Type of surgery		
Simple mastectomy	5	8.3
Quadrantectomy	55	91.7

* The same woman may have more than one comorbidity. HER2-: human epidermal growth factor receptor 2-negative.

In the reproductive profile, regarding the menopausal status at T0, 60% of the sample had regular menstrual cycles and were classified as premenopausal ($\chi^2=20.8$; $p<0.0001$). However, in T1, 15% had irregular cycles and 58.3% had amenorrhea after chemotherapy ($\chi^2=20.8$; $p<0.0001$) (Table 2).

Table 2. Characterization of variables related to the reproductive profile of women with breast cancer undergoing chemotherapy, Paraná, Brazil, 2017-2018

Characteristic	Categories	N	%	p-value*
Menopausal status T0	Premenopause	36	60	<0.0001
	Perimenopause	8	13.3	
	Postmenopause	16	26.7	
Menopausal status T1	Amenorrhea	35	58.3	0.0003
	Irregular	9	15	
	Early postmenopause	16	26.7	
Number of pregnancies	Nulliparous	3	5	0.0002
	1	12	20	
	2	25	41.7	
	3	10	16.7	
	4 or more	10	16.7	

(continues)

Table 2. Continuation

Characteristic	Categories	N	%	p-value*
Number of abortions	1	16	26.7	<0.0001
	2	1	1.7	
	3 or more	2	3.3	
Number of childbirths	1	19	31.7	<0.00001
	2	28	46.7	
	3	6	10	
	4 or more	4	6.7	
Mode of delivery**	Vaginal	37	51.4	<0.0001
	C-section	28	38.9	
	Forceps	7	9.7	

* Chi-square test for independent variables; ** It was possible to select more than one option.

By using the perinometer, values for rapid and slow contractions were obtained, and the means for T0 were 18.78cmH₂O (SD±8.32) and 21.61s (SD±12.28), and for T1, 17.85cmH₂O (SD±7.71) and 20.35s (SD±9.96). There was a statistically significant difference between the rapid contractions of T0 and T1 (p=0.002) and slow contractions of T0 and T1 (p=0.006).

Table 3. Means and standard deviations (SD) of rapid and slow contractions obtained with the perineometer in the evaluations at T0 and T1, Paraná, Brazil, 2017-2018

Characteristic	Mean (SD) T0	p-value*	Mean (SD) T1	P-value*
Rapid contractions				
Menopausal status T0				
Premenopause	19.24 (8.64)	0.986	18.4 (8.00)	0.007
Postmenopause	17.27 (7.42)		16.32 (6.86)	
Number of childbirths				
Nulliparous				
≤2	16.13 (12.60)	0.070	18.13 (15.21)	0.993
>2	19.95 (8.02)		18.82 (7.14)	
Slow contractions				
Menopausal status T0				
Premenopause	22.68 (12.36)	0.913	21.39 (9.88)	0.002
Postmenopause	18.69 (11.96)		17.51 (9.95)	
Number of childbirths				
Nulliparous				
≤2	14.92 (8.67)	0.769	14.92 (8.88)	0.218
>2	22.19 (10.20)		20.94 (8.14)	
Slow contractions				
Menopausal status T0				
Premenopause	20.91 (20.57)	0.769	19.23 (16.77)	0.218
Postmenopause	22.19 (10.20)		20.94 (8.14)	

* Factorial analysis of variance for repeated measures.

Table 4. Means and standard deviations (SD) of the menopause rating scale (MRS) and the international consultation on incontinence questionnaire - short form (ICIQ-SF) domains at the T0 and T1 evaluations, Paraná, Brazil, 2017-2018

Characteristic	Mean (SD) T0	Mean (SD) T1	P-value*
MRS Domains			
Somatic-vegetative			
Premenopause	1.20 (1.56)	5.98 (2.54)	0.571
Postmenopause	1.94 (2.11)	6.25 (3.30)	
Psychological			

(continues)

Table 4. Continuation

Characteristic	Mean (SD) T0	Mean (SD) T1	P-value*
Premenopause	1.64 (1.67)	3.57 (2.31)	0.868
Postmenopause	2.88 (3.12)	4.69 (3.07)	
Urogenital			0.638
Premenopause	1.36 (1.89)	4.41 (2.36)	
Postmenopause	1.88 (1.89)	4.62 (2.28)	
ICIQ-SF			0.532
Menopausal status T0			
Premenopause	1.50 (2.98)	2.66 (3.37)	
Postmenopause	2.00 (2.63)	2.81 (2.59)	
Number of childbirths			0.990
Nulliparous	1.67 (2.89)	2.67 (2.52)	
≤2	1.68 (3.10)	2.77 (3.43)	
>2	1.40 (1.84)	2.40 (1.96)	

* Factorial analysis of variance for repeated measures.

At T0, 35% of the women had urinary symptoms with a mild impact on QoL, and at T1 this number increased to 58% ($p < 0.05$) of women with symptoms, who, however, remained with a mild impact on QoL.

According to the qualitative question of the ICIQ-SF (“When does urine leak?”), in the evaluation at T0, 41 women (68.3%) answered that they never leak urine; while at T1 only 25 women (41.6%) denied urinary leak. An increase in episodes of urine leak associated with cough or sneezing at T1 was observed, related to stress urinary incontinence (SUI).

From the multivariate evaluation, it was verified that the first principal component was defined as the variation of the MRS scores values and the slow contraction (eigenvalue=1.61; variability=40.34%), being inversely related. The second principal component represents the association between ICIQ-SF and rapid contraction (eigenvalue=1.05; variability=26.16%), also inversely related.

Factor loadings were then evaluated regarding different factors: types of chemotherapy (Figure 1A), treatment

period (Figure 1B), menopausal status (Figure 1C) and number of childbirths (Figure 1D). It was possible to verify no distinction of the integrated behavior of the variables obtained by perineometry, MRS and ICIQ-SF between the groups of women undergoing different types of chemotherapy ($p > 0.05$), as well as no difference in relation to menopausal status ($p > 0.05$) and number of childbirths ($p > 0.05$). However, statistically significant differences were found throughout the evaluations at T0 and T1, considering the sample as a whole.

Factor loadings of principal component 1, which represent MRS and slow contraction, showed significant differences between the evaluation times ($t = 14.6$; $p < 0.0001$), showing worsening of menopausal symptoms and reduced pelvic floor muscle endurance. Factor loadings of principal component 2, which represent the ICIQ-SF and rapid contraction, showed significant differences between the evaluation times ($t = -6$; $p < 0.0001$), showing worsening of urinary symptoms and QoL and reduction of pelvic floor muscle strength at T1.

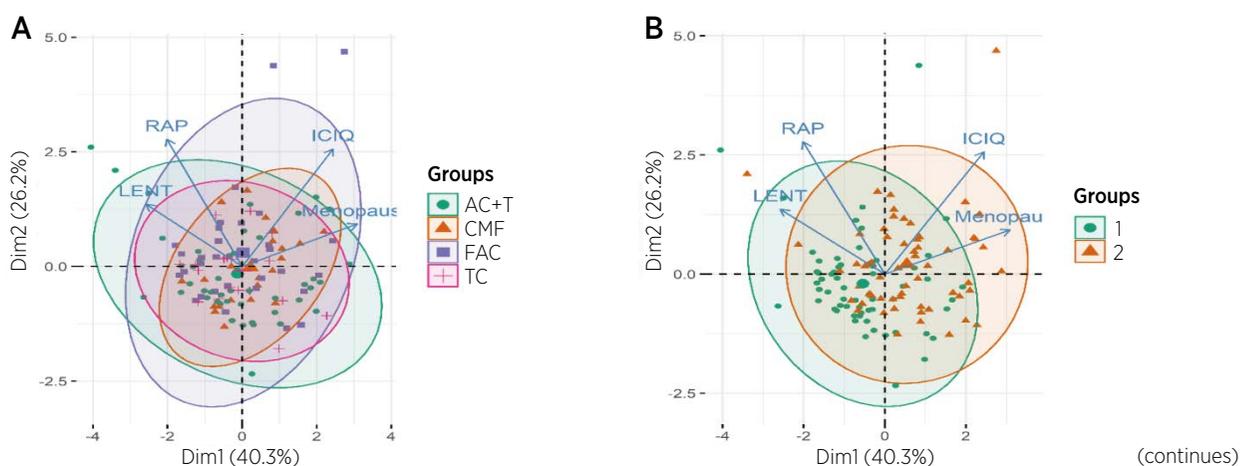


Figure 1. Ordination diagram of the principal components analysis of the variables rapid contraction, slow contraction, menopause rating scale (MRS) and international consultation on incontinence questionnaire – short form (ICIQ-SF) in relation to the groups of different (A) types of chemotherapy, (B) period of treatment, (C) menopausal status and (D) number of childbirths, Paraná, Brazil, 2017-2018

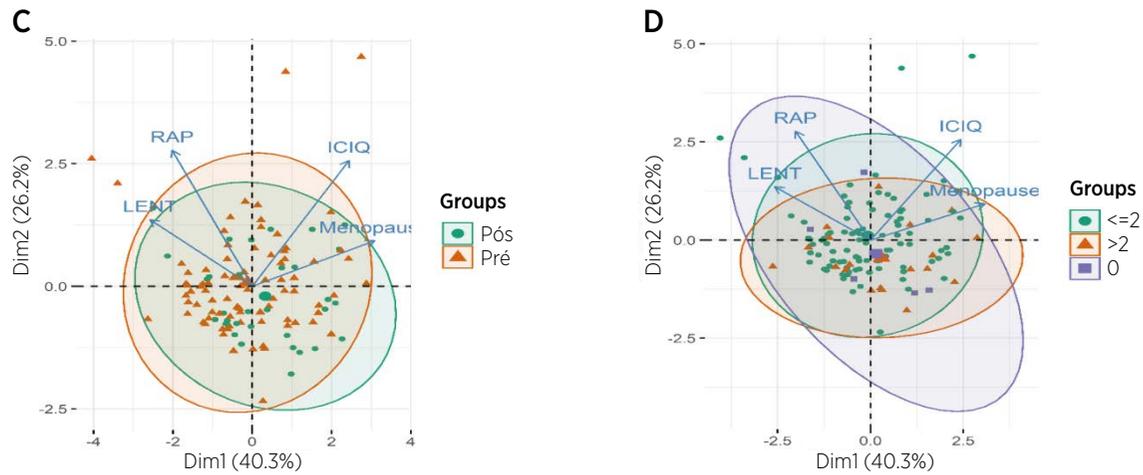


Figure 1. Continuation

RAP: rapid contraction; LENT: slow contraction; AC+T, CMF, FAC and CT: types of chemotherapy; treatment period T0 and T1; menopausal status T0 and T1; number of childbirths.

DISCUSSION

Although breast cancer occurs predominantly in women aged over 50 years and postmenopausal, this pathology diagnosis has been increasing rapidly among younger and premenopausal women¹, corroborating our study, in which the mean age was 46 years and the proportion of premenopausal women before chemotherapy was 60%.

The use of polychemotherapy drugs for cancer treatment makes it difficult to evaluate which agent is responsible for amenorrhea, but it is known that alkylating agents, such as cyclophosphamide, are associated with a higher incidence of this condition^{15,16}. Although more reliable markers for ovarian injury are available, amenorrhea is used in several studies, with or without the association of other instruments, possibly because it is an observational indicator, not generating costs or interventions. Its incidence varies from 18% to 97% according to the woman's age, with a higher probability of being irreversible from the age of 45 years and worsening with aging^{16,17}.

Due to the observation time limited to 30 days after the end of chemotherapy, it was not possible to analyze the reversibility of amenorrhea among women who were premenopausal before treatment, being a limitation of the study. It is noteworthy that, after chemotherapy, 71.7% of women remained with irregular or absent menstrual cycles, corroborating another study that evaluated ovarian function in breast cancer survivors treated with cyclophosphamide and found a significant reduction in the presence of the regular menstrual cycle: from 91% before treatment to 7% after¹⁸.

This chemotherapy-induced alteration of ovarian function may promote changes in pelvic floor tone and trophism¹⁹, reinforcing the need for evaluation of PFMs, involved in both urinary continence and sexual function. Perineometry has been used to evaluate the activity of PFMs, and studies indicate that this is a simple, reliable, well-tolerated and minimally invasive method that allows for identifying correct muscle recruitment, in addition to presenting a strong correlation with electromyographic findings^{20,21}.

To date, no studies using the perineometer to measure the strength and resistance of PFMs in women with breast cancer undergoing chemotherapy are known, which makes it impossible to compare the values found after chemotherapy. However, in comparison with healthy women aged 40 to 50 years, the mean of rapid contractions at T0 was similar to the values of another study, that reached 13.1 (SD=7.3), which, however, were lower than the mean of slow contractions found in this study²¹. This difference in values can be justified by the promotion of perineal identification promoted by the researcher in our study before data collection, through guidance and digital palpation of the muscles evaluated.

This significant reduction in the PFMs strength after chemotherapy (both in the rapid contraction, referring to the action of type II muscle fibers, and in the slow contraction, performed by type I fibers) may be associated with the harmful action of chemotherapy on the ovaries, which respond by reducing estrogen in the pelvic floor tissues, causing a reduction in muscle strength (atrophy)⁴, reinforced by the worsening of urinary symptoms observed in the ICIQ-SF.

Regarding urinary complaints, 72.5% of the participants in this study mentioned SUI, corroborating a previous study conducted with 556 women without a history of cancer attended in two urogynecology outpatient clinics²².

Urinary symptoms related to menopause include UI, increased urination frequency, nocturia, dysuria, and recurrent lower urinary tract infections, and present a positive correlation between symptom severity and sexual function⁵⁻⁷. These symptoms differ from vasomotor symptoms and, if untreated, persist throughout life and may even worsen over time²³. Regarding women with breast cancer, these symptoms may also be a result of secondary ovarian insufficiency to chemotherapy in premenopausal women and, with greater intensity, in postmenopausal women²⁴. However, this association was not observed in this study, and the impact was similar in both groups.

An increase from 35% to 58% in urinary symptoms was observed after chemotherapy, which remained mild. It is noteworthy that, in low- and medium-developed countries, 25% of women in general have pelvic floor disorders, with UI being the most frequent²⁵. In a study with 203 women with breast cancer that evaluated urinary symptoms before and three months after the start of neoadjuvant treatment, 79.8% and 87.7% prevalence, respectively, was observed²⁶. The impact of UI on women's QoL was considered moderate²⁶, corroborating this study.

Treatments for breast cancer change the hormonal environment of pre- and postmenopausal women and alter the experiences of menopausal symptoms. From 38% to 100% of them experience symptoms that negatively impact QoL^{6,27}. In this study, it was found that women after chemotherapy with cyclophosphamide presented significant worsening of symptoms in the three domains evaluated by MRS at the end of treatment and specifically of urogenital symptoms, which went from mild at T0 to severe at T1, reflecting worsening of QoL. These data are supported by a research that evaluated menopausal symptoms immediately after chemotherapy predominantly based on alkylating agents for several types of cancer, observing increased vaginal dryness after treatment ($p < 0.001$)²⁸. Genitourinary adverse events resulting from chemotherapy can be reduced and managed in most cases, but require early detection and appropriate treatment, as highlighted in previous studies^{29,30}.

Study limitations

The limitations of the study are the non-use of surface electromyography for PFMs due to the unavailability

of the device; the type of perineometer used, which was not digital; and also the non-experimental design.

CONCLUSION

The study found that women undergoing chemotherapy treatment with cyclophosphamide suffered genitourinary changes, such as reduced strength and endurance of PFMs, UI, and vulvovaginal atrophy regardless of the factors evaluated (type of chemotherapy, parity and menopausal status prior to chemotherapy).

Greater attention and discussion by multidisciplinary teams is necessary, as these symptoms can be reduced and managed in most cases, but depend on early detection, guidance and appropriate treatment.

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