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Evaluation of cardiovascular risk and metabolic syndrome in women with breast cancer using tamoxifen

Avaliação de risco cardiovascular e síndrome metabólica em mulheres com câncer de mama em uso de tamoxifeno

Abstract

Introduction: Breast cancer is the second most common cancer in the world and the most common type among women. In addition, the cardiovascular disease is the most common cause of death in women. **Objective:** The objective was to assess cardiovascular risk factors and metabolic syndrome in women with breast cancer using tamoxifen. **Methods:** Cross-sectional study conducted with women with a previous breast cancer diagnosis. For metabolic syndrome diagnosis, the criteria established by the American Heart Association (2009) were used. Cardiovascular risk was assessed using the Framingham Risk Score. **Results:** The frequency of metabolic syndrome is 75% (n=24) of the study participants. The cardiovascular risk assessment showed that 18.7% (n=6) and 21.9% (n=7) of the participants were at intermediate to high risk, respectively. **Conclusion:** It is concluded that women undergoing breast cancer treatment have a high prevalence of metabolic syndrome and cardiovascular risk factors, increasing mortality from cardiovascular diseases in this group.

Keywords: Breast Cancer. Metabolic Syndrome. Cardiovascular Disease. Risk Factor

Resumo

Introdução: O câncer de mama é o segundo tipo de câncer mais comum no mundo e o mais comum entre as mulheres. Além disso, a doença cardiovascular é a causa mais comum de morte em mulheres. **Objetivo:** Avaliar os fatores de risco cardiovascular e de síndrome metabólica em mulheres com câncer de mama em uso de tamoxifeno. **Métodos:** Estudo transversal realizado com mulheres com diagnóstico prévio de câncer de mama. Para o diagnóstico da síndrome metabólica, foram utilizados os critérios da American Heart Association (2009). O risco cardiovascular foi avaliado pelo escore de risco de Framingham. **Resultados:** A frequência da síndrome metabólica é de 75% (n=24) dos participantes do estudo. A avaliação do risco cardiovascular mostrou que 18,7% (n=6) e 21,9% (n=7) das participantes apresentavam risco intermediário a alto, respectivamente. **Conclusão:** Conclui-se que mulheres em tratamento para câncer de mama apresentam alta prevalência de síndrome metabólica e fatores de risco cardiovascular, aumentando a mortalidade por doenças cardiovasculares neste grupo.

Palavras-chave: Câncer de Mama. Síndrome Metabólica. Doença Cardiovascular. Fator de Risco.

INTRODUCTION

Breast cancer (BC) is the second most common cancer in the world and the most frequent type among women, both in developed and developing countries, with a total of 2.09 million diagnosed cases (11.6%) in 2018. Worldwide, it is ranked as the fifth leading cause of cancer death in general (627,000 deaths - 6.6%) and the most frequent cause of cancer death in women in less developed regions and the second in more developed regions, getting behind lung cancer.¹

The incidence of breast cancer increases with age, being higher in women aged 45 to 54 years (21.6% of cases), 65 to 74 years (21.9% of cases) and 55 to 64 years (25.6% of cases), the latter being the most prevalent and the average age for diagnosis equal to 61 years.²

Although the risk of breast cancer is a major concern for women, cardiovascular disease (CVD), including coronary heart disease and stroke, is the most common cause of death in women worldwide. Mortality rate increase due to CVD in certain parts of the world is recognized, and in women, there is a significant increase in the risk of developing CVD after menopause, regardless the age it occurs.³

In middle-age women, breast cancer survivors may have the same risk factors for CVD as without cancer, therefore, they represent a potential risk group for developing this condition. Higher values of total cholesterol (TC), Low Density Lipoprotein - Low density lipoprotein (LDL), and triglyceride (TG), prevalence of obesity and high blood pressure (BP) levels were observed in cancer survivor women.^{4,5}

Other findings also suggest women treated for breast cancer appear to be at additional risk of developing metabolic syndrome (MS). It is important to note that even without the manifestations of MS, women treated for breast cancer are at risk for CVD due to the high rate of comorbidities, such as obesity, systemic arterial hypertension and diabetes mellitus (DM) not related to cancer, in addition to the risk of documented CVD associated with chemotherapy (QT), radiation therapy (RXT) and endocrine therapies.⁶

Therefore, the aim of the present study was to evaluate cardiovascular risk factors and MS in women with breast cancer using tamoxifen

METHODS

This study was approved by the Research Ethics Committee (CEP) of the Hospital Universitário Antônio Pedro of the Universidade Federal Fluminense (HUAP-UFF) under the number 56257816.8.0000.5243. All study participants signed an informed consent form.

This is a cross-sectional study conducted with women with a previous breast cancer diagnosis treated at the High Complexity Assistance Unit (UNACON) at HUAP-UFF, located in the city of Niterói in the state of Rio de Janeiro. Sample data were collected from June to September 2016.

Inclusion criteria were: being female, being at least 30 years old and maximum 80 years old, who are in pre- or post-menopausal states, with a previous breast cancer diagnosis and undergoing treatment with TAM, having performed QT, RXT or breast surgery previously.

Data were collected using a standardized anamnesis protocol, applied in person. This questionnaire contained data related to patient identification, comorbidities, medication use, family history, lifestyle (physical activity), sociodemographic variables and menopausal status.

For anthropometric evaluation, the following variables were measured and collected: weight, height, body mass index (BMI) and waist circumference (WC). Weight gain was calculated from the difference between weight reported by each volunteer before treatment and final weight measured in the ambulatory. The cutoff points

proposed by the World Health Organization were used as a reference, adopting a BMI between 25.0 to 29.9 Kg / m² and ≥30, respectively, as a criterion for classifying overweight and obesity.

WC was classified according to the American Heart Association (AHA),⁷ which suggests WC <80 cm for Latin American women.

To define the lipid profile variables, blood samples were collected from the peripheral vein. The tests requested were total cholesterol (CT), triglycerides (TG), High Density Lipoprotein (HDL) and Protein C-Reactive Ultra-Sensitive (PCR). The concentration of Low Density Lipoprotein (LDL) was calculated according to the Friedewald formula, for TG values until 400 mg / dL, where $LDL = CT - HDL - TG / 5$.⁸

BP was measured using the automatic pulse monitor and the classification was made according to the VI Brazilian Guideline for Hypertension.⁹ For the diagnosis of metabolic syndrome, the criteria established by the American Heart Association⁷ were used. Cardiovascular risk was assessed using the Framingham Risk Score.¹⁰

The results were presented using descriptive statistics as mean and standard deviation (SD) or absolute and relative frequencies, according to the type of variable. For continuous variables, they were presented as mean or median±SD according to distribution, parametric or non-parametric. The prevalence of risk factors for cardiovascular disease and metabolic syndrome was calculated. These analyzes were performed using GraphPad Prism 5.0 software.

RESULTS

Thirty-two women with breast cancer with different ages and different stages of the disease were evaluated. The average age range of the sample was 59.75 ± 9.62 years of age (ranging from 42 to 76 years). The average time of TAM use was 29.62 months (ranging from 4 to 58 months). Most women from mixed ethnicity (56.2%), 43.7% (n = 14) had completed high school and 65.6% (n = 21) are post-menopausal. Regarding the lifestyle and physical activity variables, it was found that 81.2% (n = 26) of the patients did not smoke and 84.4% (n = 27) did not drink alcohol, however, 71.9% (n = 23) were sedentary. All patients who reported not practicing any type of physical activity were considered sedentary. In addition to these data, approximately 72% (n = 23) of the women assessed had a family history of cancer.

Table 1 presents data on weight gain, BMI and WC. More than half of the patients (59.4%, n = 19) presented weight gain after starting the treatment, presenting an average weight of 66.94 ± 12.16 Kg. Considering the BMI, 62.2% (n = 21) of the patients were classified as overweight and 15.6% (n = 5) were obese. In addition, 93.7% (n = 30) had some degree of abdominal obesity with WC ≥80 cm.

Tabela 1. Weight gain, BMI and waist circumference. Niterói, RJ, 2016

.Variables	Mean±SD	N	%
<i>Weight gain</i>			
Yes	-	19	59.4
No	-	13	40.6
<i>BMI (Kg/m²)</i>			
Underweight	16.95±0.00	1	3.1
Eutrophy	21.80±2.59	5	15.6
Overweight	26,67±1.39	21	62.2
Obesity	34.20±3.03	5	15.6
<i>Waist circumference (cm)</i>			
< 80 cm	70.00±4.24	2	6.2
≥ 80 cm	94.03±9.46	30	93.7

BMI - Body mass index. Data are expressed as mean ± standard deviation (SD).

Concerning MS frequency, 75% (n = 24) of women were classified as having the syndrome. In addition to WC ≥ 80 cm, other MS classification criteria, such as high blood pressure, hypertriglyceridemia and low HDL values were present in 43.7% (n = 14), 37.5% (n = 12) and 34.4% (n = 11), respectively. Regarding the presence of DM among the participants, 25% (n = 8) had a medical diagnosis and oral hyperglycemic agents and /or insulin use (table 2).

Table 2. Frequency of MS, Hipertension, DM, lipid profile and cardiovascular risk. Niterói, RJ, 2016

Variables	Mean or median \pm SD	N	%
<i>Metabolic syndrome</i>			
Yes	-	24	75
No	-	8	25
<i>Systemic Arterial Hypertension</i>			
Hypertensive (in treatment)	-	14	43.7
Non-hypertensive	-	18	56.2
<i>Diabetes mellitus¹</i>			
Yes	-	8	25
No	-	24	75
<i>Lipid profile (mg / dL)²</i>			
<i>Total cholesterol</i>			
< 200	170.11 \pm 21.94	18	56.2
≥ 200	235.43 \pm 25.49	14	43.7
<i>HDL</i>			
< 50	37.36 \pm 8.44	11	34.4
≥ 50	60.71 \pm 13.48	21	65.6
<i>Triglycerides</i>			
< 150	98.10 \pm 27.11	20	62.5
≥ 150	199.42 \pm 25.76	12	37.5
<i>LDL</i>			
< 130	98.73 \pm 20.08	22	68.7
≥ 130	163.20 \pm 19.45	10	31.2
<i>Ultra-sensitive protein C-reactive (mg/L)³</i>			
< 0.3 (mg/L)	0.11 \pm 0.08	21	65.6
≥ 0.3 (mg/L)	0.56 \pm 1.01	9	28.1
<i>Framingham Score</i>			
Low		19	59.5
Intermediate		6	18.7
High		7	21.9

HDL – high density lipoprotein; LDL – low density lipoprotein. Data are expressed as mean or median \pm standard deviation (SD).

¹Standards of Medical Care in Diabetes (2014);

²V Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose (2013);

³I Diretriz de Prevenção Cardiovascular da Sociedade Brasileira de Cardiologia (2014).

For CT, 43.7% (n = 14) had values greater than 200 mg/dL. LDL, on the other hand, had an average of 118.87 \pm 36.12 mg/dL, with only 31.2% (n = 10) of the sample showing values greater than 130 mg/dL. Regarding

inflammatory parameter, the majority (65.6%, $n = 24$) did not present high values (≥ 0.3 mg / L) of ultra-sensitive C reactive protein. Cardiovascular risk assessment using the Framingham Score showed 18.7% ($n = 6$) and 21.9% ($n = 7$) of the participants with risk between intermediate and high, respectively.

DISCUSSION

The participants in the present study had an average age of 59.75 years of age. According to the literature, the highest occurrence of BC is in the age group 45 to 65 years old.^{2,11,12} Regarding ethnicity, the population of women was mostly mixed or white. Lagares et al.,¹³ in their study showed a higher prevalence of white women (62.5%), which demonstrates a great miscegenation of ethnicities in the Brazilian population, as evidenced by Oliveira et al.,¹⁴ where most women were mixed and black (68.75%). When assessing participants educational level, 43.7% ($n = 14$) had completed high school and only four (12.5%) had completed higher education. In the studies by Leite et al.,¹¹ and Lagares et al.,¹³ it was observed most of the participants had incomplete primary education and the highest prevalence was in lower economic classes (D and C). According to Liu et al.,¹⁵ the socioeconomic level reflects directly on the prognosis since among patients with a low-income occupation or group with a lower educational level, the diagnosis of the tumor was later, implementation rates of relevant investigations were lower, as were rates of radiotherapy, chemotherapy and hormone therapy.

Concerning physical activity, in the present study 71.9% ($n = 23$) of the participants were sedentary. Nahas et al.,⁶ also observed in their study more than 80% of women with postmenopausal breast cancer were considered sedentary, not performing any type of regular physical activity. Other studies have also found a high frequency of physical inactivity among breast cancer patients.^{6,16-18}

Regarding anthropometric data, it was observed in the present study that more than half of the patients presented weight gain after starting the treatment (59.4%, $n = 19$). Nahas et al.,⁶ in their study also observed weight gain that occurred after diagnosis, which averaged 4.7 kg over an average time of 9.1 ± 4.0 years, reflecting a significant increase in BMI. This result is similar to that observed by Thomson et al.¹⁹

In the present study, 62.2% of patients were overweight while 15.6% were obese according to the BMI classification. According to Picon-Ruiz et al.,²⁰ in a systematic review, they observed that the increase in overweight and obesity affected between 50% and 96% of women with breast cancer. Also according to this author, the weight gain observed was greater in pre-menopausal women, in those treated with chemotherapy and in overweight women at the time of diagnosis.

In the work of Zanchini et al.¹⁸ and Kolling et al.,²¹ a prevalence of postmenopausal women was observed, as well as a high percentage of patients overweight, with a mean BMI greater than 25 kg/m². Such data corroborate to the present study data, where it is possible to identify a higher percentage of postmenopausal women (65.6%, $n = 21$) and a higher prevalence of overweight and obesity.

Therefore, it is observed patients weight gain with breast cancer after diagnosis can be considered multifactorial, being influenced by the patient's condition before diagnosis, pre and post-menopausal status and type of treatment. In addition, it can also be associated with complications after primary and reconstructive surgery, increased fatigue, decreased physical activity and psychological and physical treatment stress.^{6,22} The importance of a multidisciplinary follow-up with these patients is also highlighted, aiming to prevent weight gain during treatment.

Along to excess weight presented by the patients, it was also observed that 93.7% ($n = 30$) had waist circumference greater than 80 cm. These results corroborate to several studies in the literature.^{6,14,17,23-26}

In addition to WC, other classification criteria for MS were assessed. The group of patients presented 43.7% of people with systemic arterial hypertension being treated.⁷ Regarding the occurrence of DM in the group, 25% (n = 8) had the disease diagnosed and under treatment.

Regarding the biochemical profile, 37.5% of the patients had triglycerides in a concentration greater than 150 mg/dL (mean plus standard deviation of 199.42 ± 25.76), 34.4% (n = 11) had HDL values less than 50 mg/dL (mean plus standard deviation of 37.36 ± 8.44).

According to American Heart Association⁷ criteria, 75% (n = 24) of the patients were diagnosed with MS. Healy et al.,²⁷ in their study pointed out a 39% prevalence of MS among 105 women with a recent diagnosis of postmenopausal breast cancer. These results corroborate with other studies pointing to a high prevalence of MS in breast cancer patients.^{16,19,28}

In the present study, among diagnostic criteria for MS, the most prevalent was abdominal obesity, affecting 93.7%, followed by hypertension (43.7%). In a Brazilian study, evaluating 81 women with a recent breast cancer diagnosis, MS occurrence was observed in 59.2%, with central obesity (86.4%) and hypertension (60.5%) also being the most prevalent criteria.²⁸ In the study by Buttros et al.,¹⁶ the most frequent criteria were central obesity (62.5%) and hypertriglyceridemia (45.2%), whereas in the study by Thonsom et al.,¹⁹ abdominal obesity was the most frequent criterion (96%) followed by a 65% reduction in HDL.

According to the study by Dibaba et al.,²⁹ MS was related to an increased mortality risk for patients with BC. The risk of mortality from BC increased significantly with the increase in the number of components of MS, with an increase of more than three times the risk of mortality from BC among women with four components of MS compared to women with none. In addition, the association of WC greater than 80 cm, systemic arterial hypertension and high TC was strongly associated with an increased risk of mortality.³⁰

This risk increases exponentially in women over 60 years of age and in those who are postmenopausal, while the data in pre-menopausal women are still not sufficiently elucidated.^{31,32} The pathways explaining a worse prognosis of BC in patients with MS involve hyperinsulinemia, promoting tumor growth, angiogenesis and metastasis and has anti-apoptotic properties.³³

Central obesity (elevated WC) and related increased adiposity can intensify aromatase activity, which converts androgens to estrogen, a hormone promoting breast tumors growth and tumor cells survival, in addition to being related to the risk of insulin resistance, glucose intolerance, high blood pressure and dyslipidemia.^{34,35}

In the present study, CRP values were above reference value in only 27.28% of patients, with mean of 0.56 ± 1.01 mg / dL. According to Nahas et al.,⁶ and Thomson et al.,¹⁹ the average CRP values was higher in women with MS compared to women without MS. The high CRP values may reflect the fact the women participating in the present study were overweight or obese, with increased abdominal fat and, consequently, high levels of systemic inflammatory markers for CVD, in addition to the presence of MS.

Finally, it was observed 18.7% (n = 6) of the participants with intermediate cardiovascular risk while 21.9% (n = 7) had a high risk according to Framingham Score. In the study by Anderson et al.,³⁶ an increase in cardiovascular risk was observed in women in the post-menopausal period. Gernaat et al.,¹⁰ on the other hand, did not observe differences between climacteric status for cardiovascular risk, increasing, however, the risk among patients who had breast CA compared to those who did not.

In a systematic review, Gernaat et al.,¹⁰ pointed to higher risk of mortality from cardiovascular disease among women with breast cancer with more advanced age at diagnosis, tumor position, diagnosis in previous period and black ethnic origin

CONCLUSION

In view of the above, it is concluded that women undergoing BC treatment have a high prevalence of MS and cardiovascular risk factors. Patients at high cardiovascular disease risk identification is important to optimize prevention, reduce mortality and adapt breast cancer treatment.

STRENGTHS AND LIMITATIONS

The research group did not find in the literature Data on the risk of cardiovascular disease and metabolic syndrome in Brazilian women with cancer and, even with the nutritional monitoring carried out at the nutrition and oncology clinic at HUAP, many do not accept to participate in the research making the data collection more difficult in a more representative sample of this population

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Contributors

Fiochi RSF participation in data collection, analysis and interpretation, participation in writing the study and participation in final review and approval of the manuscript for submission; Cardoso LMF and Monnerat JAS participation in writing the study and participation in final review and approval of the manuscript for submission; Huguenin GVB participation in the idealization of the study design and participation in data collection, analysis and interpretation; Rocha GS and Barroso SG participation in the idealization of the study design, participation in data collection, analysis and interpretation and participation in final review and approval of the manuscript for submission.

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