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Prevalence and influence of overweight and obesity on clinical and epidemiological profile of breast cancer patients in the North of Mato Grosso, Brazil: a retrospective cross-sectional study

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Abstract. Obesity is one of the main preventable risk factors in post-menopausal breast cancer. This retrospective cross-sectional study aimed to demonstrate the clinical and epidemiological profile of breast cancer patients diagnosed in the period from 2013 to 2018 in the North of Mato Grosso, Brazil and to verify the prevalence and influence of overweight and obesity in these patients. Data were collected from patient's medical records who were diagnosed with breast

carcinoma in the Department of Oncology of Santo Antônio's Hospital, in Sinop-MT. 196 patients were included. 99.5% were women. The majority were married, ≥50 years old (57.7%) and overweight or obese. In the overweight and obesity group the percentage of patients with invasive breast carcinoma were significantly higher when compared with eutrophic group (p=0.03). In all groups the profile of estrogen and progesterone receptors positive and HER-2 negative were more prevalent, however, the frequency of triple negative profile was higher in the overweight (7.1%) and obesity (6.3%) group when compared with control (4.3%) group, as well as the presence of hypertension and diabetes. In conclusion, it was observed a high prevalence of overweight and obesity in breast cancer patients, which contributed to modify the histological type of breast cancer (high prevalence of invasive and lobular carcinomas), increase the frequency of patients in stages 3 and 4, the percentage of triple negative profile and the frequency of other comorbidities, as hypertension and diabetes. Furthermore, metformin, an antidiabetic drug, seems to be contributing to reduce tumor development and improve the clinical profile and prognosis in diabetic breast cancer patients.
Keywords: Cancer, Breast cancer, Overweight, Obesity, Prognosis.

Introduction

Cancer's global incidence and burden has been rising rapidly, with a large impact on mortality and quality of life (MATTIUZZI; LIPPI, 2019). This is a result from the population aging and changes in the incidence and distribution of cancer risk factors, which are closely associated with economic development (BRAY *et al.*, 2018a). Although inherent risk factors play an important role in carcinogenesis, extrinsic risk factors are especially relevant because they are modifiable – 35% of cancer-related deaths in the world could have been prevented by lifestyle changes and reducing other external agents (LEWANDOWSKA *et al.*, 2019). The major risk factors include smoking, alcohol consumption, low physical activity, diabetes mellitus, obesity and a high-fat and low-fiber diet (QUEIROZ et al., 2022; LEWANDOWSKA et al., 2019; MARTIN; MCGEE, 2018; VINEIS; WILD, 2014).

Breast cancer is one of the most relevant types of cancer in the world, both in incidence and mortality (CANCER TODAY, 2022); it is responsible for 11.6% of all cancers, ranking number one in women in many countries, and responsible for 6.6% of all cancer-related deaths (AHMAD, 2019). The high incidence of breast cancer cases, as in all cancer cases, is due to lifestyle changes, but also due to more screening programs, especially in developing countries (QUEIROZ et al., 2022; HARBECK; GNANT, 2017). These countries, while suffering an increase in breast cancer cases, also uphold the lowest survival rates (AKRAM *et al.*, 2017). In Brazil, there are 66 thousands new breast cancer cases estimated for each year of 2020-2022, representing 29.2% of all cancer types in women (the most incident besides non-melanoma skin cancer)(INCA, 2019a). Furthermore, in Brazil, the rate of mortality for breast cancer in 2018 was of 11.7/100,000 habitants (BRAY *et al.*, 2018b).

The minority of breast cancer cases is attributable to an inherited mutation, with lifestyle and environmental factors playing a major role in its genesis (ROJAS; STUCKEY, 2016). The female sex is the main risk factor, followed by age: women between 40 to 60 years have the highest incidence (SUN *et al.*, 2017). Since estrogen (endogenous or exogenous) is an important factor, reproductive features that increase the estrogenic exposure (e.g. nulliparity, early menarche, late menopause, obesity) will also increase the chances of breast cancer (SUN *et al.*, 2017).

Obesity is one of the main preventable risk factors in post-menopausal breast cancer, while decreasing the risk in pre-menopausal women (QUEIROZ et al., 2022; PICON-RUIZ et al., 2017; WINTERS et al., 2017; FORTNER et al., 2016; CALLE; KAAKS, 2004). The main reason behind this association after menopause is an increase in the levels of endogenous estrogens, as a result from higher aromatase activity in the excessive adipose tissue. Furthermore, the hyperinsulinemia, frequently present in obesity, contribute to decrease the synthesis of sex-hormone-binding globulin (SHBG), thus increasing the bioavailability of sex-hormones, like estrogens (oestrone) and testosterone. Consequently, these hormones can interact with its receptors leading to cell proliferation and tumor development (CALLE; KAAKS, 2004). This seems to be especially relevant in the context of hormone-receptor positive tumors, and women who haven't used hormone replacement therapy (FORTNER *et al.*, 2016).

Another important mechanism linking obesity to breast cancer is the chronic low-grade inflammation (ARGOLO; HUDIS; IYENGAR, 2018), contributing to create an tumor microenvironment that favors tumor development, survival, invasion and metastasis (DENG *et al.*, 2016). The accumulation of adipose tissue leads to an inflammatory process, increasing the levels of some adipocytokines, as leptin, and decreasing the levels of adiponectin (QUEIROZ et al., 2022; CALLE; KAAKS, 2004). Adiponectin act as a protective factor, while higher leptin levels predict poorer breast cancer outcomes (ARGOLO; HUDIS; IYENGAR, 2018; PARIDA; SIDDHARTH; SHARMA, 2019). In addition, obesity influences on the patient's prognosis, increasing the risk of recurrences and even death (JIRALERSPONG; GOODWIN, 2016). Women with high body mass index (BMI) suffer from more complications from mastectomy, needs higher doses of radiation, and present an inferior response to chemotherapy and endocrine therapy, even with adequate treatment regimens (LEE *et al.*, 2019). Thus, the present study aimed to demonstrate the clinical and epidemiological profile of breast cancer patients diagnosed with this type of cancer in the period from 2013 to 2018 (6 years) in the North of Mato Grosso state, Brazil, as well as verify the

prevalence and influence of overweight and obesity in these individuals.

Materials and Methods

Study type

This is a retrospective cross-sectional study with data collected by the patient's medical records whom were diagnosed with breast carcinoma in the period from January 1st, 2013 to December 31st, 2018, in the Department of Oncology of Santo Antônio's Hospital (SAH) (Sinop, Mato Grosso (MT), Brazil), a cancer referral service in the North of Mato Grosso state, which is a public-private institution, that perform outpatient care for the Unified Health System (Sistema Único de Saúde – SUS) for the city of Sinop and region. Sinop is within the five biggest cities of MT, located approximately 500 km from the capital Cuiabá, with a population of 146,005 habitant (IBGE, 2021a).

Gathering and data analysis

It was included all patient's medical records that was diagnosed with breast cancer from 2013 to 2018 and treated at the SAH in Sinop-MT. The identities of research's subjects were kept anonymous and were collected only the medical record's numbers. All data were collected from patients who were consulted by SUS.

The data gathering was realized by the full reading and analysis of each patient's medical records. The recording of the data was done electronically, using the Microsoft® Excel® spreadsheet software (Office 365), and organized in charts with de following informations according to sociodemographic and clinical variables: gender, civil status, city that was living (place of origin), state (citizenship), age, body mass index (BMI), diagnosis, type of breast cancer, cancer staging, types of treatment, antineoplastic and other medicines used by the patient, presence of other diseases (as cardiovascular diseases, diabetes), presence of metastasis and prognosis. The data were collected during the period from 2017 to 2020.

The results were analyzed as a descriptive analysis, evaluating the frequency of distribution and the data were presented as percentage (%), these analysis and tables were performed using the Excel® spreadsheet software. n denotes the number of medical records used. Thus, the prevalence of breast cancer and overweight and obesity in these patients was evaluated.

To evaluate the influence of overweight and obesity on the prognosis of patients, assessing the correlation between a BMI ≥ 25.0 kg/m^2 with staging, presence of other comorbidities, presence of metastasis and patient death, the patient data were divided into three groups: *Eutrophic Group (non-obese*): Breast cancer patients who had a BMI between 18.6 and 24.9 kg/m^2; *Overweight Group*: Breast cancer patients who had a BMI ≥ 25.0 and <30 kg/m^2 and; *Obese Group*: Breast cancer patients who had a BMI ≥ 30.0 kg/m^2.

Then, the following data were evaluated between these three groups: patient age, BMI, staging, number of deaths, number of patients presenting metastasis, presence of diabetes and cardiovascular disease, receptor expression, and type of treatment performed.

Data were presented as mean ± standard deviation (SD) or as %. The results were statistically evaluated by One-Way ANOVA test and Tukey posttest (multiple comparisons test) for the quantitative analysis of continuous variables or by chi-square test (χ^2) or Fisher test in the case of analysis of categorical variables. The analysis were carried out using the GraphPad Prism® 7 Program. The minimum acceptable significance level was $p<0.05$.

Ethical aspects

The ethical aspects considered were the ones from the 466/2012 Resolution, of the Brazilian Ministry of Health, that estipulate the ethical standards that regulate the research that implicate humans. The study execution was initialized after the authorization released by the Medical's Ethics Committee of SAH's, and after approval of the project by the accountable Oncology doctors. The project was also approved by the Ethics Committee for Human Study at Universidade Federal de Mato Grosso (protocol nº 3.636.390).

Results and discussion

Prevalence of overweight and obesity

196 patients diagnosed with breast cancer and attended in the Department of Oncology of SAH, in Sinop-MT between the period of 2013 and 2018 were included in this study. Results demonstrated that 99.5% of patients were women, following the tendency of this pathology, and only 1 male patient (0.5%) was diagnosed and treated during this period (Table 1). According to data from the National Cancer Institute (INCA, 2019b), 16,927 deaths from breast cancer were recorded in Brazil in the year of 2017, and 16,724 (98.8%) of which were female.

In accordance with age, it was observed that most patients were over 50 years old (57.7%), being in accordance with the literature data that demonstrate age as an important risk factor for breast tumor development (SUN *et al.*, 2017).

Concerning the body mass index (BMI), 32.7% of patients were obese, 21.4% were overweight and 23.5% were eutrophic, demonstrating a significant prevalence of overweight and obesity in this group of patients; unfortunately in 22.4% of patient's medical records was not informed the values of BMI, thus, for future analysis it was only considered the data from 152 patients that presented BMI values or body weight and height values in yours personal records, which was used to calculate the BMI. Evaluating the presence of other comorbidities, it was observed that 34.7% of patients presented hypertension and 9.2% presented diabetes.

Table 1. Distribution of patients diagnosed with breast cancer in 2013-2018 according to clinical profile. Department of Oncology from Santo Antônio's Hospital, Sinop-MT.

Variable	No	Percentage (%)
Gender		
Female	195	99.5
Male	1	0.5
Age Range (Years)		
≤50	83	42.3
>50	113	57.7
BMI Range		
Eutrophic	46	23.5
Overweight	42	21.4
Obese	64	32.7
Not informed	44	22.4
Diabetes		
Yes	18	9.2
No	141	71.9
Not informed	37	18.9
Hypertension		
Yes	68	34.7
No	94	48.0
Not informed	34	17.3
Types of Breast Cancer		
Ductal and Lobular carcinoma (Mixed)	9	4.6
Ductal Carcinoma in situ	10	5.1
Ductal Carcinomas	80	40.8
Lobular Carcinomas	11	5.6
Invasive Carcinomas	50	25.5
Others	36	18.4
Tumor Stage		
1 and 2	124	63.3
3 and 4	70	35.7
Not mentioned	2	1.0
Metastasis		
Present	43	21.9
Not present	148	75.5
Not mentioned	5	2.6
Prognosis		
Follow up	133	67.8
Deaths	47	24.0
Continued treatment in another service	15	7.7
Abandonment	1	0.5
Total	**196**	**100.0**

In general, the ductal carcinoma was the most frequent type of breast cancer observed in the present study (40.8%), similarly to the literature data, and invasive carcinoma was the second most frequent type of cancer diagnosed in the patients, representing 25.5% (1/4) of all breast cancer types (Table 1). 63.3% of patients were in stages I and II at the diagnostic and 35.7% were in stages III and IV. 21.9% of patients presented metastasis and 24.0% died. 67.8% (n=133) of patients were in follow up, 7.7% (n=15) followed the treatment in another service and 0.5% (n=1) abandoned the treatment (Table 1). Thus, it was observed that most patients were in stages I and II, which reflect the better prognosis of these patients presenting a relative low frequency of metastasis (21.9%) and low frequency of deaths (24%).

The survival rate of 76% observed in the present study agrees with other study developed in Goiania-GO, Brazil, once they demonstrated a survival rate of 72.1% (DE FREITAS JÚNIOR et al., 2017) and it is in accordance with our previous study that demonstrated a survival rate of 74.28% and 22.85% of deaths (CHIARADIA et al., 2021), in patients diagnosed with breast cancer in 2012. On the other hand, other studies demonstrated higher percentage of survival rate, as Siegel et al. (2012)(SIEGEL et al., 2012) that observed a 90% of survival rate in patients diagnosed with breast cancer. These differences and similarities may be mediated by several factors, as differences in treatment availability, treatment adherence, stage at diagnosis, among others.

Sociodemographic data of eutrophic, overweight and obese breast cancer patients

Analyzing the patients in accordance with its BMI values, 152 patients were included in the study.

100% were women. The majority were married (61.2%), ≥50 years old (55.26%) and overweight or obese (69.7%) (Table 2).

There was no significant difference between these groups when the gender, civil status, city, and citizenship were analyzed (Table 2). Most women were from Sinop-MT, in all groups, and concerning citizenship, most patients were from Paraná state (southern region of Brazil) 41.30% (eutrophic), 35.8% (overweight) and 32.8% (obese group)(Table 2). This result may be a consequence of the policy of occupation used in Sinop-MT, part of a project to occupy the Brazilian Legal Amazon (IBGE, 2021b).

As mentioned before, in accordance with the civil status, no significant difference was observed between the groups, being the married women the majority. Similar data were found in a previously published study by our group (CHIARADIA *et al.*, 2021). Soares et al. (2012)(SOARES *et al.*, 2012) also demonstrated that most women diagnosed with breast cancer was married.

Table 2. Distribution of patients diagnosed with breast cancer in 2013-2018 according to eutrophic, overweight and obese groups, and their sociodemographic characteristics. Department of Oncology from Santo Antônio's Hospital, Sinop-MT.

Variable	Eutrophic N (%)	Overweight N (%)	Obese N (%)	Total N (%)	*p*
	46 (30.3)	**42 (27.6)**	**64 (42.1)**	**152 (100)**	
Gender					
Female	46 (100.0)	42 (100.0)	64 (100.0)	152 (100)	0.95
Male	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Civil Status					
Married	32 (69.6)	22 (52.4)	39 (60.9)	93 (61.2)	0.40
Divorced	1 (2.2)	5 (11.9)	6 (9.4)	12 (7.9)	
Single	6 (13.0)	6 (14.2)	5 (7.8)	17 (11.2)	
Widower	3 (6.5)	7 (16.7)	7 (10.9)	17 (11.2)	
Others	4 (8.7)	2 (4.8)	7 (10.9)	13 (8.6)	
City (Origin)					
Sinop	20 (43.5)	18 (42.9)	30 (46.9)	68 (44.7)	0.88
Sorriso	7 (15.2)	9 (21.4)	8 (12.5)	24 (15.8)	
Lucas do Rio verde	1 (2.2)	2 (4.8)	3 (4.7)	6 (3.9)	
Others	18 (39.1)	13 (31.0)	23 (35.9)	54 (35.5)	
State (Citizenship)					
Paraná	19 (41.3)	15 (35.8)	21 (32.8)	55 (36.2)	0.47
Rio Grande do Sul	8 (17.4)	6 (14.3)	7 (10.9)	21 (13.8)	
Santa Catarina	2 (4.3)	5 (11.9)	8 (12.5)	15 (9.9)	
São Paulo	3 (6.5)	3 (7.1)	4 (6.3)	10 (6.6)	
Rio de Janeiro	0 (0.0)	0 (0.0)	2 (3.1)	2 (1.3)	
Goiás	1 (2.2)	3 (7.1)	0 (0.0)	4 (2.6)	
Mato Grosso	2 (4.3)	3 (7.1)	9 (14.1)	14 (9.2)	
Mato Grosso do Sul	3 (6.5)	1 (2.4)	6 (9.4)	10 (6.6)	
Other States	7 (15.2)	6 (14.3)	6 (9.4)	19 (12.5)	
Non mentioned	1 (2.2)	0 (0.0)	1 (1.7)	2 (1.3)	

Statistical analysis: Chi-square test (χ^2).

Clinical and treatment profile of breast cancer patients

Breast cancer has a lot of risk factors as female sex, obesity, family history, genetics, age and others (QUEIROZ et al., 2022; ROJAS; STUCKEY, 2016). Aging is a well-known risk factor for it (ANGULO *et al.*, 2013). In the present study, most of the diagnosed cases of breast cancer happened over 50 years. In the overweight and obese groups, 61.9% and 62.5% of women was above 50 years old, on the other hand, in the eutrophic group 60.9% of patients were under 50 years old (p = 0.03)(SUN *et al.*, 2017). It is in agreement with the literature data that demonstrates that the accumulation of adipose tissue, and consequently the overweight and obesity condition, increases the risk of breast cancer in post menopause, which frequently occur after 50 years old (CALLE; KAAKS, 2004).

After menopause the adipose tissue is one of the most important tissue responsible to synthetize estrogen, because the expression of aromatase enzyme. Thus, the excess of adipose tissue in overweight or obese individuals contribute to the production of estrogen in high quantity, consequently stimulating cell proliferation. Furthermore, as mentioned in the introduction section, the hyperinsulinemia, frequently present in obesity, contribute to decrease the synthesis of sex-hormone-binding globulin (SHBG), thus increasing the bioavailability of sex-hormones, like estrogens (oestrone) and testosterone. Consequently, these hormones can interact with its receptors leading to cell proliferation and tumor development (CALLE; KAAKS, 2004).

The origin of breast tumor cells can be of the epithelium of the ducts or the mammary lobules (ANGULO *et al.*, 2013), being the ductal breast

cancer the most prevalent type according to the available literature (ANGULO *et al.*, 2013). In our study, the ductal was the most common type of breast cancer in the eutrophic group (54.3%), however, in the overweight and obese groups the most prevalent type was invasive carcinoma (45.2% and 39.1%, respectively) (p=0.03). Furthermore, it was demonstrated a proportional decrease in the frequency of ductal and lobular carcinoma (mixed), ductal carcinoma *in situ* and ductal carcinoma, and an increase in the frequency of lobular carcinoma and invasive carcinoma of breast cancer in the overweight and obese group when compared to the eutrophic group (Table 3). This demonstrates that overweight/obesity is contributing to the development of breast cancer and with a more aggressive behavior profile. A secondary analysis of the Women's Health Initiative Randomized clinical trials showed that obesity was associated with a greater risk for invasive breast cancer, advanced disease, tumor size and lymph nodes positivity (NEUHOUSER *et al.*, 2015).

Profile of receptors expressed by the tumor cells has important prognosis and therapeutic implications. Estrogen and progesterone are steroidal hormones that act by stimulating gene transcription, protein synthesis and cell proliferation (DRÃGÃNESCU; TRESTIOREANU; CARMOCAN, 2017).

The human epidermal growth factor receptor 2 (HER-2) also stimulates cell proliferation, as well as, cell invasion and angiogenesis (SUN *et al.*, 2017). There are target therapies for these receptors (SUN *et al.*, 2017). In the present study, in all groups, the most common type of breast cancer presented estrogen and progesterone receptor positive expression and HER-2 negative expression (ER+, PR+ and HER2-), which contribute to the treatment protocol using hormone therapy.

On the other hand, the triple negative profile was greater in the overweight (7.1%) and obese (6.3%) groups than in the eutrophic group (4.3%), which can lead to a worst prognosis, once this triple negative profile presents a more aggressive behavior decreasing the patient's survival and leasing options of treatment (LIBSON; LIPPMAN, 2014). In accordance with Chácon and Costanzo (2010)(CHACÓN; COSTANZO, 2010) some factors can be associated with this triple negative profile, as increased body weight, first birth at a young age, lack of breastfeeding and use of oral contraceptives before the age of 40. Thus, it suggests that the overweight/obesity condition is contributing with this more aggressive profile. In fact, it was observed that in a total of 9 patients that presented the triple negative profile (Table 3), 6 died (66.7%), being 5 (83.3%) overweight/obese and 1 (16.7%) from the eutrophic group (Table 7).

Concerning the tumor stages, in the overweight and obese groups, 48.8% and 43.8% of patients, respectively, were diagnosed at the advanced stages (3 and 4) while in the eutrophic group 37.0% were diagnosed as stages 3 or 4. Although there was a difference in the frequency between the groups (11.8% and 6.8% higher in the overweight and obese group when compared to the eutrophic group, respectively), this result was not statistically significant (p = 0.53)(Table 3). However, when analyzing the clinical profile of patients that died, it was observed that the majority of overweight/obese group (90%) was in stages 3 and 4 of tumor development (p=0.04) (Table 7).

There was no difference between the groups in relation to the type of treatment used (p = 0.99). All modalities of treatment, as chemotherapy, hormone therapy, radiotherapy, and surgery, was used by the patients, being chemotherapy and surgery, the most frequent types of treatment used. Furthermore, most patients of all groups used the combination of all therapeutics modalities, and almost all patients (98.0%) realized chemotherapy treatment (exclusive or in association with other modalities of treatment) (Table 3).

In the present study, the most prevalent chemotherapy medicines used were doxorubicin (76.97%), cyclophosphamide (85.52%), paclitaxel and docetaxel (45.39% and 25.65%, respectively) (Table 4). In hormone therapy, tamoxifen was the most used modality (59.21%) (Table 4). Once the chemotherapy causes a lot of side effects that are harmful to the maintenance of treatment and for the quality of life, it was used adjuvant drugs. Most adjuvant drugs used by the patients were ondansetron and dexamethasone, both antiemetic drugs (Table 4).

There are several modalities of treatment. Hormone therapy with tamoxifen or anastrozole, for example, acts blocking or decreasing the estrogen action in the cells. Radiotherapy and conserving surgery in early stage of breast cancer are widely accepted because they allow organ preservation and excellent outcomes (CASTANEDA; CLINICS; 2017). Finally, chemotherapy can be used in an adjuvant way (after the surgery) or neoadjuvant way (before the surgery). In the present work, most patients used the combination of all therapeutics modalities, demonstrating how challenging the management of this pathology is, and ~98% of patients used chemotherapy in your treatment protocol, showing the importance of the use of antineoplastic drugs for the treatment.

According to The National Comprehensive Cancer network guidelines there are adjuvants chemotherapy regimens recommended. In the AC-T regimen, occurs the sequential or simultaneous administration of anthracycline, cyclophosphamide and taxane. Other options include cyclophosphamide, methotrexate and fluorouracil (FUJII *et al.*, 2015). In our study, the most prevalent antineoplastic chemotherapy drugs used were doxorubicin (anthracycline), cyclophosphamide, paclitaxel, and docetaxel (both taxanes). These agents, who compose the AC-T regimen, are the most accepted drugs for adjuvant chemotherapy of breast cancer.

Table 3. Distribution of patients diagnosed with breast cancer in 2013-2018 according to eutrophic, overweight and obese groups and their clinical characteristics. Department of Oncology from Santo Antônio's Hospital, Sinop-MT.

Variable	Eutrophic N (%)	Overweight N (%)	Obese N (%)	Total N (%)	*p*
	46 (30.3)	**42 (27.6)**	**64 (42.1)**	**152 (100)**	
Age Range (Years)					
≤50	28 (60.9)	16 (38.1)	24 (37.5)	68 (44.7)	0.03
>50	18 (39.1)	26 (61.9)	40 (62.5)	84 (55.3)	
Types of Breast Cancer					
Ductal and Lobular carcinoma (Mixed)	3 (6.5)	0 (0.0)	3 (4.7)	6 (4.0)	0.03
Ductal Carcinoma in situ	2 (4.3)	1 (0.9)	0 (0.0)	3 (2.0)	
Ductal Carcinomas	25 (54.3)	15 (35.8)	21 (32.8)	61 (40.1)	
Lobular Carcinomas	0 (0.0)	3 (7.1)	8 (12.5)	11 (7.2)	
Invasive Carcinomas	9 (19.6)	19 (45.2)	25 (39.1)	53 (34.9)	
Others	7 (15.2)	4 (9.5)	7 (10.9)	18 (11.8)	
Receptors Expression (ER/PR/HER2)					
Positive- Positive- Negative	29 (63.04)	26 (61.9)	39 (60.9)	94 (61.8)	0.92
Negative-Negative- Negative (Triple negative)	2 (4.3)	3 (7.1)	4 (6.3)	9 (6.0)	
Positive- Negative-Positive	2 (4.34)	0 (0.0)	4 (6.3)	6 (4.0)	
Positive- Positive- Positive	5 (10.86)	6 (14.2)	8 (12.5)	19 (12.5)	
Others	8 (17.39)	7 (16.7)	9 (14.1)	24 (15.7)	
ER positive					
Yes	41 (91.1)	35 (83.3)	54 (90.0)	130 (88.4)	0.47
No	4 (8.9)	7 (16.7)	6 (10.0)	17 (11.6)	
PR positive					
Yes	39 (86.7)	34 (81.0)	49 (81.7)	122 (83.0)	0.73
No	6 (13.3)	8 (19.0)	11 (18.3)	25 (17.0)	
HER2 expression					
Yes	9 (22.0)	9 (23.0)	15 (25.4)	33 (23.7)	0.92
No	32 (78.0)	30 (77.0)	44 (74.6)	106 (76.3)	
Tumor Stage					
1 and 2	29 (63.0)	21 (50.0)	36 (56.3)	86 (56.6)	0.53
3 and 4	17 (37.0)	20 (48.8)	28 (43.8)	65 (43.0)	
Type of Treatment					
Chemotherapy	44 (95.7)	42 (100.0)	63 (98.4)	149 (98.0)	0.99
Hormone Therapy	30 (65.2)	27 (64.3)	41 (64.1)	98 (64.5)	
Radiotherapy	28 (60.9)	25 (59.5)	44 (68.8)	97 (63.8)	
Surgery	41 (89.1)	35 (83.3)	56 (87.5)	132 (86.8)	
Treatment Protocol					
Chemotherapy Exclusive	1 (2.2)	4 (9.5)	2 (3.1)	7 (4.6)	0.60
Chemotherapy + Surgery	10 (21.7)	4 (9.5)	8 (12.5)	22 (14.5)	
Chemotherapy + Hormone Therapy	0 (0.0)	1 (2.4)	2 (3.1)	3 (2.0)	
Chemotherapy + Hormone Therapy + Surgery	6 (13.0)	7 (16.7)	8 (12.5)	21 (13.8)	
Chemotherapy + Hormone Therapy + Surgery + Radiotherapy	21 (45.7)	18 (42.9)	28 (43.8)	67 (44.0)	
Chemotherapy + Surgery + Radiotherapy	4 (8.69)	6 (14.2)	12 (18.8)	22 (14.5)	
Chemotherapy + Hormone Therapy + Radiotherapy	3 (6.5)	1 (2.4)	3 (4.7)	7 (4.6)	

Statistical analysis: Chi-square test (χ^2). ER – estrogen receptor; PR – progesterone receptor; HER-2 – human epidermal growth factor receptor 2.

Hormone therapy prevents the interaction between estrogen and tumor cells through blocking its production by aromatase inhibitors (for example, anastrozole) or blocking the action of estrogen in its receptor (for example, tamoxifen). The first class can be used only by post-menopausal women. The second one had shown benefit even after the end of the treatment protocol and additive benefit to chemotherapy (DRÃGÃNESCU; TRESTIOREANU; CARMOCAN, 2017). Over half of our patients had used tamoxifen therapy.

It is well known that antineoplastic drugs can induce several side effects, such as nausea and vomiting, anemia, alopecia, hepatotoxicity, nephrotoxicity, among others, and these unpleasant symptoms reduce the quality of life of patients

undergoing cancer therapy (YEO *et al.*, 2020). In this way, the control of these symptoms is essential for the treatment adherence. There are several drugs that can be used for this aim, for example, ondansetron (CLAVEL; SOUKOP; ONCOLOGY, 1993) and dexamethasone. In our study, 98.7% of patients used ondansetron and 88.8% used dexamethasone.

Table 4. Distribution of the medicines used during chemotherapy cycles. Department of Oncology from Santo Antônio's Hospital, Sinop-MT.

Variable	Eutrophic N (%)	Overweight N (%)	Obese N (%)	Total N (%)	*p*
	46 (30.3)	**42 (27.6)**	**64 (42.1)**	**152 (100)**	
Chemoterapy Medicines					
5-Fluorouracil	5 (10.9)	5 (11.9)	7 (10.9)	17 (11.2)	0.13
Cyclophosphamide	40 (87.0)	35 (83.3)	55 (85.9)	130 (85.5)	
Doxorubicin	37 (80.4)	30 (71.4)	50 (78.1)	117 (77.0)	
Herceptin® (Transtuzumab)	1 (2.2)	8 (19.1)	11 (17.2)	20 (13.2)	
Paclitaxel	24 (52.2)	12 (28.6)	33 (51.6)	69 (46.0)	
Docetaxel	8 (17.4)	17 (40.5)	14 (21.9)	39 (26.0)	
Hormone Therapy Medicines					
Tamoxifen Exclusive	28 (60.9)	25 (59.5)	39 (60.9)	92 (60.5)	0.93
Anastrozole Exclusive	3 (6.5)	1 (2.4)	3 (4.7)	7 (4.6)	
Unrealized up to now	15 (32.6)	14 (33.3)	23 (35.9)	52 (34.2)	
Adjuvants					
Omeprazole	1 (2.2)	2 (4.8)	1 (1.6)	4 (2.6)	0.73
Diphenhydramine	26 (56.5)	30 (71.4)	40 (62.5)	96 (63.2)	
Ranitidine	7 (15.2)	12 (28.6)	23 (35.9)	42 (27.6)	
Nausedron® (Ondansetron)	45 (97.8)	41 (97.6)	64 (100.0)	150 (98.7)	
Decadron® (Dexamethasone)	41 (89.1)	36 (85.7)	58 (90.6)	135 (88.8)	

Clinical and prognostic profile of breast cancer patients

In our study, hypertension was found in 20.9% of eutrophic patients, 44.7% of overweight and 50.9% of obese patients (p = 0.008). Diabetes mellitus was found only in the overweight and obese groups, with a prevalence of 8.1% and 18.2% (p = 0.009), respectively (Table 5). There was no statistical difference in the metastasis (p = 0.79) and deaths (p = 0.92) between the groups (Table 5).

Several studies have been demonstrating that obesity increase the development of several comorbidities, as diabetes, dyslipidemia, hypertension and several types of cancer (AVGERINOS et al., 2019)(KOPELMAN, 2000). In the present study, it was demonstrated that the overweight and obese breast cancer patients also presented higher prevalence of other comorbidities, as hypertension and diabetes, both pathologies that can influence both carcinogenesis and the morbidity/mortality for breast cancer, either by itself or by its complications in target organs. Furthermore, studies demonstrates that high blood pressure by itself can increase the risk of breast cancer by 15% (HAN *et al.*, 2017; SERAVALLE; GRASSI, 2017), thus this could suggest an even higher risk of breast cancer in patients with both diseases.

As mentioned above, diabetes mellitus was found only in the overweight and obese groups. Studies have shown a 16% prevalence of diabetes in breast cancer patients and indicated that this is a risk factor for a higher incidence and poorer prognosis in breast cancer cases (SAMUEL *et al.*, 2018). A meta-analysis, however, suggested that this association could be derived from the higher adiposity in diabetic women, being obesity the main influencing risk factor (BOYLE *et al.*, 2012). This is in accordance with the present study, once that, when it was compared the three groups: eutrophic breast cancer patients, overweight/obese breast cancer patients (without diabetes) and overweight/obese breast cancer patients with diabetes (Table 6), the last group do not present a worst clinical profile and prognosis. On the contrary, the overweight/obese patients (without diabetes) presented a worst clinical profile (Table 6).

It was observed a significantly difference in age (p=0.0012), body weight (p<0.0001) and BMI (p<0.0001) in patients overweight/obese and diabetic when compared with eutrophic groups, being these results significantly higher when compared with eutrophic values (Table 6). The type

of breast cancer (0.0049), tumor stage (0.0048), presence of hypertension (p<0.0001) and metastasis (0.0279) (Table 6) were different between the groups, being worst in overweight/obese breast cancer patients (without diabetes), except for hypertension, once the prevalence of hypertension was significantly higher in patients with both pathologies (obesity and diabetes). Thus, demonstrating that both obesity and diabetes, in fact, increase the risk for arterial hypertension (Table 6). As described in table 6, 20.9% of eutrophic patients, 31.3% of overweight/obese patients and 91.3% overweight/obese and diabetic patients presented hypertension, p<0,0001. No difference was observed in the variables: receptor expression profile, HER2 expression and death (Table 6).

One possible mechanism that can be contributing with this better results in patients with diabetes is the use of metformin (an antidiabetic drug) widely used for treatment of type 2 diabetes and that have been demonstrating a significant antitumor effect both *in vivo* and *in vitro* (QUEIROZ *et al.*, 2015)(QUEIROZ *et al.*, 2014)(MIRANDA *et al.*, 2014)(FONSECA *et al.*, 2011)(SAHRA *et al.*, 2010). It was observed that only patients with diabetes had the use of metformin described in the patient's medical records. Furthermore, it was observed that between 13 patients with diabetes, 10 have been using metformin as antidiabetic therapy, and all of them was in stage 1 or 2 of tumor development, as well as none was died during the period of this study.

Several studies have been demonstrating the antitumor effect of metformin, both *in vivo* (QUEIROZ, E. A. *et al.*, 2015)(FONSECA *et al.*, 2011) and *in vitro* (QUEIROZ, E. *et al.*, 2014). Queiroz et al. (2014) demonstrated that metformin significantly reduces MCF-7 breast cancer cell proliferation due to cell cycle arrest and apoptosis, effects mediated by AMPK (AMP-activated protein kinase) and FOXO3a (Forkhead transcription factor 3a) activation and oxidative stress.

Queiroz et al. (2015) and Fonseca et al. (2011) also demonstrated a significant antitumor effect of metformin on obese and non-obese rats with Walker-156 tumor, mechanism associated with a direct and indirect antitumor effect. Indirect effect mediated by the metabolic effects of metformin improving the lipid profile, reducing the accumulation of periepididymal and retroperitoneal adipose tissue and reducing lipid peroxidation (FONSECA *et al.*, 2011), as well as direct antitumor effect increasing apoptosis of tumor cells by activation of AMPK and FOXO3a and decreasing the insulin signaling pathway (QUEIROZ, E. A. *et al.*, 2015).

Table 5. Distribution of patients diagnosed with breast cancer in 2013-2018 according to eutrophic, overweight and obese groups and other diseases presents in the patients and their clinical prognosis. Department of Oncology from Santo Antonio's Hospital, Sinop-MT.

Variable	Eutrophic	Overweight	Obese	Total	*p*
N (%)	**46 (30.3)**	**42 (27.6)**	**64 (42.1)**	**152 (100)**	
Systemic Arterial Hypertension					
Yes	9 (20.9)	17 (44.7)	28 (50.9)	54 (39.7)	0.008
No	34 (79.1)	21 (55.3)	27 (49.1)	82 (60.3)	
Diabetes mellitus					
Yes	0 (0.0)	3 (8.1)	10 (18.2)	13 (9.6)	0.009
No	43 (100.0)	34 (91.9)	45 (81.8)	122 (90.4)	
Metastasis					
Yes	11 (23.9)	11 (26.2)	19 (29.7)	41 (27.0)	0.79
No	35 (76.1)	31 (73.8)	45 (70.3)	111 (73.0)	
Deaths					
Yes	13 (28.3)	11 (26.2)	19 (29.7)	43 (28.3)	0.92
No	33 (71.7)	31 (73.8)	45 (70.3)	109 (71.7)	

Statistical analysis: Chi-square test (χ^2).

Obesity and diabetes are risk factors for breast cancer because they causes chronic low-grade inflammation, insulin resistance, hyperinsulinemia, oxidative stress and higher bioavailability of hormones, as estrogen (ROJAS; STUCKEY, 2016; ANGULO et al., 2013). These factors can contribute with the three stages of carcinogenesis, especially promotion and progression stages (QUEIROZ *et al.*, 2022; ANGULO et al., 2013; CALLE; KAAKS, 2004). Thus, the effects of metformin controlling these adverse metabolic effects frequently present in obesity and diabetes can contribute to reduce the tumor development, as observed in this study.

Table 6. Clinical profile of eutrophic, overweight/obese and overweight/obese diabetic breast cancer patients. Department of Oncology from Santo Antonio's Hospital, Sinop-MT.

Variable	Eutrophic patients N (%)	Overweight/ Obese patients N (%)	Overweight/ Obese and Diabetic patients N (%)	Total N (%)	*p*
N (%)	**43 (31.9)**	**79 (58.5)**	**13 (9.6)**	**135 (100)**	
Age (years)	48 ± 10	55 ± 11**	55 ± 7	53 ± 11	0.0012
Weight (kg)	59.5 ± 7.3	77.1 ± 11.7***	82.5 ± 11.5***	72 ± 14	<0,0001
BMI (kg/m^2)$^{\&}$	23.3 ± 1.5	31.4 ± 4***	33.8 ± 3.8***	29 ± 5	<0,0001
Types of Breast Cancer$^{\#}$					
Ductal and Lobular carcinoma (Mixed)/ Ductal Carcinoma in situ/ Ductal Carcinomas	28 (70.0)	28 (38.4)	5 (41.7)	61 (48.8)	0.0049
Lobular Carcinomas/ Invasive Carcinomas/ Others	12 (30.0)	45 (61.6)	7 (58.3)	61 (51.2)	
Receptors Expression (ER/PR/HER2)					
Positive- Positive- Negative	28 (65.1)	42 (53.2)	12 (92.3)	82 (60.7)	0.0930
Negative-Negative- Negative (Triple negative)	2 (4.7)	7 (8.9)	0 (0.0)	9 (6.7)	
Others	13 (30.2)	30 (38.0)	1 (7.7)	44 (32.6)	
HER2 expression$^{\#}$					
Yes	9 (23.1)	21 (26.3)	1 (7.7)	31 (23.5)	0.3416
No	30 (76.9)	59 (73.8)	12 (92.3)	101 (76.5)	
Tumor Stage$^{\#}$					
1 and 2	28 (65.1)	37 (47.4)	12 (92.3)	77 (57.5)	0.0048
3 and 4	15 (34.9)	41 (52.6)	1 (7.7)	57 (42.5)	
Systemic Arterial Hypertension					
Yes	9 (20.9)	25 (31.3)	12 (92.3)	46 (33.8)	<0.0001
No	34 (79.1)	55 (68.8)	1 (7.7)	90 (66.2)	
Metastasis					
Yes	9 (22.0)	31 (38.8)	1 (7.7)	41 (30.6)	0.0279
No	32 (78.0)	49 (61.3)	12 (92.3)	93 (69.4)	
Death					
Yes	11 (25.6)	25 (31.3)	1 (7.7)	37 (27.2)	0.2001
No	32 (74.4)	55 (68.8)	12 (92.3)	99 (72.8)	

Groups: Eutrophic patients (BMI ≥ 18.6 and ≤ 24.9 kg/m^2), Overweight/Obese patients (patients with BMI ≥ 25 kg/m^2 and without diabetes) and Overweight/Obese and Diabetic patients (patients with BMI ≥ 25 kg/m^2 and with diabetes diagnosis). In the eutrophic group the survival time of patients that died (n=11) was 40±21 months, in the overweight/obese was 32±22 (n=79), and in the diabetic patient that died had a survival time of 11 months and was in stage 4 of tumor development. Statistical analysis: One-Way ANOVA and Tukey posttest; $^{\&}$ Kruskall-Wallis test and Dunn´ post test; and Chi-square test (χ^2).

In table 7 is described the clinical profile of control and overweight/obese breast cancer patients who died. It was observed that the mean of survival time in months for these patients was similar between the groups, being 37 ± 21 months for eutrophic group and 29 ± 17 months for overweight/obese group (p=0.24) (Table 7).

Results demonstrated that most patients presented BMI ≥ 25 kg/m^2 (69.8%). In addition, in the overweight/obese group there was statistical difference and higher frequency of invasive carcinoma (p=0.0001), advanced tumor stages (3 and 4) (p = 0.04) and presence of hypertension when compared to the eutrophic group. No statistical difference was observed for receptors expression, presence of diabetes and presence of metastasis between the groups. Furthermore, as expected it was observed that the patients who died, in fact, presented a tumor with more aggressive behavior, as invasive carcinoma, advanced stages (3 and 4) and presence of metastasis (Table 7).

Table 7. Clinical profile of eutrophic and overweight/obese breast cancer patients who died. Department of Oncology from Santo Antonio's Hospital, Sinop-MT.

Variable	Eutrophic N (%)	Overweight/ Obese N (%)	Total N (%)	*p*
N (%)	**13 (30.2)**	**30 (69.8)**	**43 (100)**	
BMI (kg/m^2)	22.5 ± 1.5	31.7 ± 3.6	28.9 ± 5.3	<0.0001
Survival Time (Months)	37 ± 21	29 ± 17	32 ± 19	0.24
Types of Breast Cancer#				
Ductal and Lobular carcinoma (Mixed)/ Ductal Carcinoma in situ/ Ductal Carcinomas	10 (76.9)	4 (13.3)	14 (32.6)	0.0001
Lobular Carcinomas/ Invasive Carcinomas/ Others	3 (23.1)	26 (86.7)	29 (67.4)	
Receptors Expression (ER/PR/HER2)				
Positive- Positive- Negative	7 (53.8)	14 (46.7)	21 (48.8)	0.55
Negative-Negative- Negative (Triple negative)	1 (7.7)	5 (16.7)	6 (14.0)	
Others	5 (38.5)	11 (36.7)	16 (37.2)	
Tumor Stage#				
1 and 2	6 (46.2)	4 (13.3)	10 (23.3)	0.04
3 and 4	7 (53.8)	26 (86.7)	33 (76.7)	
Systemic Arterial Hypertension				
Present	2 (15.4)	14 (46.7)	16 (37.2)	0.04
Not present	10 (76.9)	12 (40.0)	22 (51.2)	
Diabetes mellitus				
Present	0 (0.0)	1 (3.3)	1 (2.3)	0.99
Not present	12 (92.3)	25 (83.3)	37 (86.0)	
Metastasis				
Present	10 (76.9)	26 (86.7)	36 (83.7)	0.99
Not present	2 (15.4)	4 (13.3)	6 (14.0)	

Statistical analysis: Chi-square test (χ^2) and Student T test.

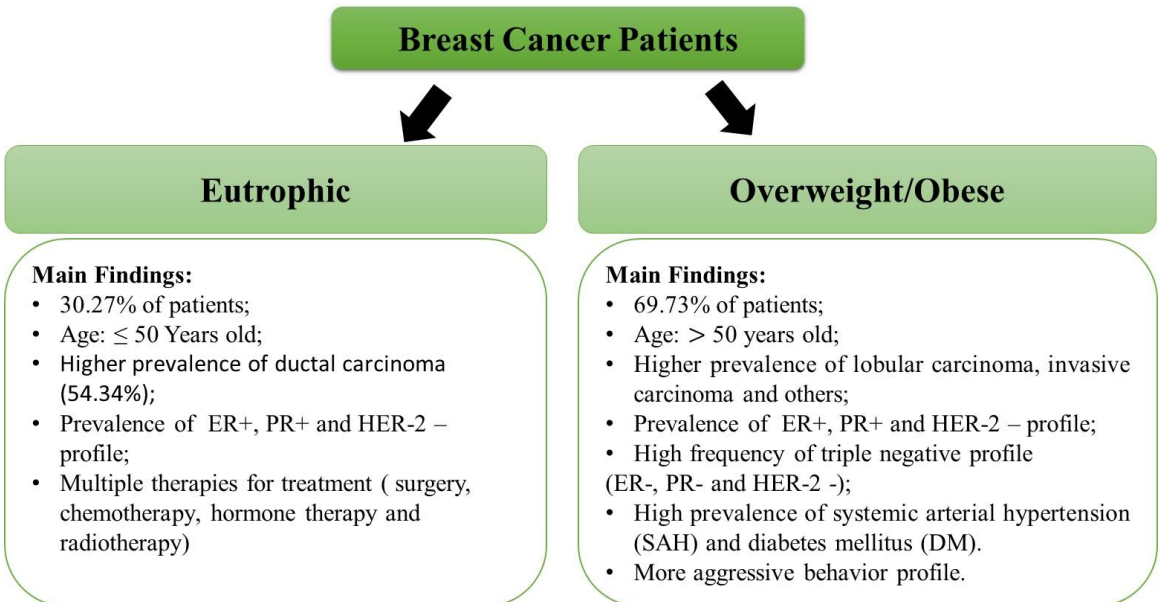

Figure 1. Schematic representation of the epidemiological and clinical profile of eutrophic and overweight/obese breast cancer patients in the North of Mato Grosso state, Brazil.

Conclusion

In conclusion, it was observed a high prevalence of overweight and obesity in breast cancer patients, which contributed to modify the histological type of breast cancer (high prevalence of invasive and lobular carcinomas), increase the frequency of patients in stages 3 and 4, the percentage of triple negative profile and the frequency of other comorbidities, as hypertension and diabetes (Figure 1). Furthermore, metformin seems to be contributing to reduce tumor

development and improve the clinical profile and prognosis of diabetic breast cancer patients.

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