An evaluation of metabolic, dietetic, and nutritional status reveals impaired nutritional outcomes in breast cancer patients undergoing chemotherapy compared with a matched control group.

Bruna Ramos da Silva¹, Sarah Rufato¹, Mirele S. Mialich¹, Loris P. Cruz², Thais Gozzo², Alceu A. Jordão¹

¹Department of Health Sciences, Ribeirão Preto Medical School. University of São Paulo (USP), Ribeirão Preto, São Paulo, Brazil.
²Nursing School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil.

Corresponding author: Bruna Ramos da Silva, ORCID iD: 0000-0002-8674-5753 (bruna.ramos.silva@usp.br). Bandeirantes Ave, 3900 – Postal code: 14049-900 - Ribeirão Preto, São Paulo, Brazil.
Abstract

Purpose: Nutritional status changes in breast cancer patients during treatment are prevalent. However, the metabolic implications of those alterations are poorly understood. We aimed to characterize body composition, lipids, glucose levels, and indices that express cardiovascular risk in breast cancer patients after completion of chemotherapy and then to compare those results with a matched control group. Methods: A cross-sectional study was performed. Women who completed their chemotherapy were recruited (BC group) and compared with a group of non-malignant age- and body mass index-matched (MC group), as well as a group of healthy, non-malignant women (HC group). Body composition by bioelectrical impedance analysis, handgrip strength, and blood sample were collected. Visceral adiposity, triglyceride glucose and lipid accumulation product indices were calculated. Food consumption was assessed. Results: 88 women were included (BC=36, MC=36, HC=16). BC patients demonstrated worse values of phase angle, nutritional risk index, extracellular body water to total body water ratio and lower handgrip strength. Additionally, those women had impairments in lipids, worst glucose levels, visceral fat dysfunction and consequently higher cardiovascular risk, presenting important unhealthy dietary patterns with higher carbohydrate and caloric intake and insufficient protein and fiber ingestion. No differences were observed between MC and HC. Conclusion: Breast cancer patients present unhealthy metabolic, nutritional, and dietetic features when compared to a group of age- and BMI-matched non-malignant females. Also, breast cancer patients had higher levels of cardiovascular risk. Further investigations are required to examine the underlying mechanisms and the potential longitudinal changes during surveillance time.

Keywords: Early breast cancer; cardiovascular risk; nutritional status; metabolic changes.
Introduction

Breast cancer is the most diagnosed cancer across the world, with more than 2.2 million cases in 2020 \(^1\). Likewise, in Brazil breast cancer was one of the most diagnosed cancers in 2020 with 66,280 new cases \(^2\). Although breast cancer is the main prevalent form of cancer, it has one of the best survival rates as well. In Brazil, the relative survival rate of 5 years between 2005 to 2009 was 87% \(^3\), whereas high-income countries presented 85% to 90% during 2010 through 2014 \(^4\). Considering the risk factors, this tumour is strongly associated with obesity and unhealthy body composition at the diagnosis \(^4\), however, weight gain and fat mass increase can be enhanced after treatment \(^5\).

Not only adiposity factors are subject to alterations by cancer treatment, but several other nutritional indicators, as lean mass, and sarcopenia \(^6\), and functional capacity measured by Hand Grip Strength (HCS) \(^7\) can also be affected. Phase angle (PhA), obtained by bioelectrical impedances, is considered both a prognosis and survival marker \(^8\)–\(^10\) and might be related to inflammatory and oxidative impairments \(^11\). Its alteration has already been demonstrated as linked to an increased nutritional risk measured by the Nutritional risk index (NRI) after cancer treatment in breast cancer patients \(^12\).

Similarly, metabolic changes are another possible consequence for those patients, such as lipids and glucose levels increase \(^13\)–\(^14\). Moreover, Godinho-Mota et al (2020) reported a visceral fat dysfunction among breast cancer patients after chemotherapy \(^15\). Considering visceral fat accumulation, the adiposity indices as the visceral adiposity index (VAI), lipid accumulation product index (LAP), and triglyceride glucose index (TyG), could be important metabolic alterations tracking tools \(^16\)–\(^20\). Furthermore, in a previous study, our research group found a metabolic syndrome prevalence of more than 50% of breast cancer survivors \(^21\), and the
combination of those alterations with unhealthy body composition and improperly food intake might lead to the development of secondary illness, for instance, the cardiovascular diseases in breast cancer survivors 22–24, reflecting directly to the survival rates and clinical evolution after the cancer care. However, worsening in blood pressure and metabolism components are commonly identified in the association with other conditions besides cancer and the treatment, such as age, body mass index (BMI), dietetics imbalance 25. In particular, obesity role plays as a trigger for these alterations, in which widespread obesity is related to the increasing metabolic syndrome (MetS) cases 26.

Accordingly, a comparison group is important in order to identify whether the bad outcomes are associated with breast cancer and the treatment, or it is associated with age, BMI, and body fat mass amount, once those characteristics are also associated with breast cancer incidence 27. We hypothesized that breast cancer patients would demonstrate impairments in lipids, glucose, and body composition, which would be worse in patients compared to a matched control group of non-malignancy history females. We further hypothesized that these impairments may be explained by the presence of unhealthy body composition and dietetic inadequacy. In order to contribute to this field of knowledge, this study aims comprehensively characterize metabolism components in breast cancer patients post-chemotherapy, and to compare body composition, metabolic profile, and food intake results to non-malignant females of similar age and BMI. We also aimed to compare breast cancer patients and matched control females to a reference group of nonmalignant, healthy normal BMIs females.

Methods

Study Population
A cross-sectional study was performed. This study involved 88 participants: 36 patients diagnosed with early breast cancer after 1 month of chemotherapy completion (BC females), 36 non-malignant females of similar age and BMI (MC females) and 16 as a reference group of nonmalignant, healthy females (HC females) with normal BMIs (normal range). The data collection for BC was made 1 month after finalizing the chemotherapy and before the hormone therapy started, due to the possible association between hormone therapy and the increase of metabolic alterations \(^{28}\). None of the participants have received nutritional counselling. Breast cancer patients were recruited through clinical oncology practices at Mastology ambulatory of General Hospital of School of Medicine of Ribeirão Preto, São Paulo, Brazil. During the clinical consultation, a responsible nurse informed the patient about the study. Those who were interested in knowing more about it were forwarded to talk to the study researcher. Women who met the following inclusion criteria were enrolled in the study: age \(\geq 18\) years and \(<65\) years; a histological confirmed diagnosis of early breast cancer (range of stage I – III); completion of the breast cancer chemotherapy treatment course. Patients who previously have already received or started chemotherapy in any other moment of life; with any type of diabetes (type 1, type II or had diabetes gestational); those fitted with a defibrillator, cardiac pacemaker, metal implants or those with a local infection/wound preventing the use of bioelectric impedance analysis pads, those unable to use a handheld dynamometer due to a neuromuscular disorder were all excluded. It was adopted the breast cancer patient data collection with 1 month after finalized the chemotherapy due to the possible association between hormone therapy and the increase of MetS risk \(^{28}\). Thus, to study only the effect of chemotherapy on the sample, the evaluation was made before the hormone therapy starting to avoid possible bias.
Women in both control groups (MC and HC) were recruited at the same hospital, the participants were employees. For both groups (BC and CG) potential participants were weighed and measured to determine BMI and completed a Health Status Screening Form to determine if they had any prior cancer or were under hormone or any other medication which could modify the metabolism that would have excluded them from participating in the study. Table 1 shows all the inclusion and exclusion criteria among the groups.

Table 1: Eligibility criteria for all participant groups.

| Criteria                  | Breast Cancer Patients | Matched Control | Health Control |
|---------------------------|------------------------|-----------------|----------------|
| Inclusion Criteria        |                        |                 |                |
| Age                       | > 18 years old         | Within ± 3 years of matched patient | > 18 years old < 60 years old |
| BMI                       |                        | Within ± 2kg/m² of matched patient |               |
| Sex                       | female                 | female          | female         |
| Clinical characteristics: |                        |                 |                |
| Cancer diagnosis          | Recent diagnosis of breast cancer without previous chemotherapy | No history of cancer | No history of cancer |
| cancer stage              | Clinical stages I-III | After completion of chemotherapy OR finished chemotherapy course |               |
| Treatment                 |                        |                 |                |
| Exclusion criteria        |                        |                 |                |
| Metastasis                |                        |                 |                |
| Previous diagnosis of cancer |                      |                 |                |
| Diabetes any type         |                        |                 |                |
| HIV                       |                        |                 |                |
| thyroid disease that is not currently managed with medication | | | |
| Pregnancy                 |                        |                 |                |
| BIA exclusion factors     |                        |                 |                |
| Uncontrolled BP           |                        |                 |                |

Captions: BMI: Body mass index; BP: Blood Pressure.
After screening, the participants eligible for the study were scheduled for the data collection visit. The Institutional Review Board at the University of São Paulo, General Hospital, approved the current study, protocol number: HCRP 14608/2017.

**Data Collection**

All participants underwent anthropometric assessments, bioelectrical impedance analysis, handgrip strength test, food intake; and blood chemical analyzes were collected. Socioeconomic, demographic, behavioral, clinical, and therapeutic data were collected directly from participants using questionnaires or obtained from medical records in the BC group. In addition, written informed consent was obtained at the begging of the visit. After 3 weeks of the data collection, a dietary food record was collected by phone call.

**Anthropometric Assessments**

Measured anthropometric characteristics include body weight, body height, waist (WC), and hip circumference (HC) as proposed by Lohman. Body mass index (BMI) was calculated as the ratio between the body weight and the height squared (kg/m²). Interpretation of these results followed the international classification proposed by the World Health Organization.

**Bioelectrical impedance analysis**

Body composition was assessed by using the bioelectrical impedance multiple-frequency (BIS) analysis (Body Composition Monitor – Fresenius Medical Care®), with different frequencies (5 to 1,000 kHz). The BIS analysis provided data regarding fat mass (FM), fat-free mass (FFM), phase angle (PhA), total body water (TBW), extracellular water (EW) and intracellular water (IW). It was calculated the ratio between EW and TBW as well. For the PhA, it was considered as worse values < 5.6°, and for the ratio between EW and TBW the overhydrated was considered as ECW/TBW ≥0.4.
Handgrip Strength

Handgrip strength (HGS) was assessed by the CharderMG4800 dynamometer. Participants were asked to sit comfortably with their shoulder adducted and forearm neutrally rotated, elbow flexed to 90°, and forearm and wrist in a neutral position using the dominant hand or contralateral side to mastectomy, in the adjuvant cases, and lymphedema (BC group). The highest value of the three tests was used for the analysis. The interpretation of muscle weakness followed the classification proposed by a Brazilian cohort, in which values below < 16kg were classified as weakness. It was considered as “yes” for the weakness group participants whose HGS values were below the cutoff.

Dietary data collection

The collection of dietary data occurred through a 24-hour food record for the study. It was collected 2 dietary records: the first one was collected on the day of the study visit and the second was collected after 3 weeks. The specific time frame was from the time the participant awoke in the morning until the time they slept at night. For this method it was used the methodology of the triple-pass 24-hour recall according to Nightingale et al, to improve the accuracy for quantification of the recall. The results obtained by the recall were inserted in the brazilian nutritional software Diet Box® to calculate the total amount of ingested energy and macronutrients. This software uses the Brazilian table of food composition in the assessment.

Reported values were analyzed by the Multiple Source Method (MSM) to estimate the usual intake distribution for daily-consumed nutrients. The MSM is a statistical method proposed in Europe by a German team which accessible is through an open source online platform. By the probability of consumption and the amount consumed and regressions models, it corrects the within-person variance of the food intake results obtained by the record and yet it generates the
usual intake for each participant [43]. Prior studies have shown that the MSM is an useful tool that provides usual nutrient and food intake estimates [44,45], thus, in order to improve the accuracy of the food consumption collected data, the MSM was applied. For the protein requirements and adequacy it was used for breast cancer patients the recommendation of 1.2 g/kg, as proposed by ESPEN guidelines 36. For the fiber requirements and adequacy, it was used for adult female recommendations being 25 g/d, according to a review with definitions and regulations for dietary fiber based on official recommendations by dietary reference intakes (DRIs) 37.

**Blood biochemical analysis**

For the blood biochemical analysis it was asked to all groups, to fast for 12 hours previously. During the study visit at the hospital a nurse collected a 9ml tube of peripheral blood for the BC group and a researcher nurse collected it for MC and HC groups. This sample was processed in the nutrition and metabolism laboratory. The peripheral blood was collected, and serum was used for the following analysis: Albumin (AL); Total protein (TP); C-reactive Protein (CRP); fasting glucose (FG); Triglycerides (TG); High-density lipoprotein (HDL); total cholesterol levels (CT). For the low-density lipoprotein (LDL) it was used the Friedwald equation 38.

**Nutritional Risk Index (NRI)**

The nutritional risk index was proposed in 1988 39 in order to assess the nutritional status of participants through albumin levels. In 2005, this index was modified 40, introducing the ideal body weight into the formula. The NRI was calculated following the equation:

\[ \text{NRI} = (1.519 \times \text{serum albumin, g/dL}) + \{41.7 \times \text{present weight (kg)/ideal body weight(kg)}\} \]

The ideal body weight was calculated using the Lorentz formula for females 41:
Ideal weight = (height − 100) − ((height − 150)/2). In those cases that body weight was over than ideal weight, the fraction present weight (kg)/ideal body weight(kg) was adopted as 1. Risk stratification the NRI for malnutrition was classified as:

- normal risk (≥100);
- mild risk (97.5 ≤ NRI<100);
- moderate risk (83.5≤ NRI <97.5);
- severe risk (NRI <83.5). It was considered as “no” for patients with nutritional risk group, participants whose NRI values were below the cutoff (<100).

**Visceral Adiposity Index, Lipid Accumulation Product Index and Triglyceride Glucose Index.**

Metabolic disorders, insulin resistance, visceral fat dysfunction and lipid over accumulation were used to assess cardiovascular risk by using the triglyceride glucose index (TyG), visceral adiposity index (VAI), and lipid accumulation product index (LAP). TyG was calculated as described by Simental-Mendia et al (2008), according to the formula: TyG index = Ln (Natural logarithm) [(TG(mg/dL) × FG(mg/dL)/2]. VAI was calculated according to the formula for women: VAI = (WC(cm)/(36,58+(BMI *1.89) *(TG/0.81) *(1.52/HDL), and LAP was calculated according to the formula for women LAP= [waist (cm)−58] × TG concentration (mmol/l). For TyG index was considered as cutoff for metabolic syndrome and insulin resistance values >8.45 for females. VAI index classification considered as being “metabolically healthy” was defined as VAI <1.59, and “metabolically unhealthy” as VAI ≥1.59. For LAP index classification it was considered LAP >30.40 as metabolically unhealthy.

**Blood pressure**

The blood pressure (BP) was evaluated using automated cuff, the Omron device (HEM-7200) from the Omron 7000 line. Two measures were taken 60 seconds apart and repeat until both measures are within 6 mmHg for both systolic and diastolic.
Statistical Analysis

The sample size calculation was performed using G*Power software version 3.1.9.4, taking into consideration the effect of chemotherapy on lipids status. The effect size of 0.575 showed that with a significance level of 95% and statistical power of 80%, using a Student t-test for paired data with a 2-sided significance level of .05. The minimum number of participants required was 29. Characteristics were summarized with the use of descriptive statistics such as mean, standard deviation (SD), median, and percentage. Shapiro-Wilk test was used to verify the distribution of continuous variables. Paired t-tests to compare the BC group to matched MC group, and two-tailed two-sample t-tests were used to compare BC group to HC group as well as MC females to HC females to analyze whether there was a statistically significant difference among the mean values of the variables of interest and to compare the differences among the groups. The analysis was run twice: the first test was considered the entire data, and in the second the outliers were removed. The results were the same for both, therefore the outliers did not influence the results reported. A level of significance was set at 0.05, and SAS Studio on SAS Institute Inc. 2015. SAS/IML® 14.1 User's Guide was used for all data analysis.

Results

Regarding the BC group, 36 females were included, 67% were Stage II, 28% were Stage III, and there were 5.5% at Stage I. The mean age was 45 years old (range, 26 – 64 years old), and the majority of women was younger than 50 years (69.5%). The prescribed protocol of treatment was the combination among Doxorubicin, Cyclophosphamide, and Docetaxel (AC-T). Clinic characteristics of the BC group are shown in table 2.

Table 2: Sample clinic characteristics.

| Variables       | N | %  |
|-----------------|---|----|
| Cancer stage    |   |    |
Chemotherapy
Neoadjuvant 25 69%
Adjuvant 11 31%

Expected cycle numbers
4* 1 3%
8 35 97%

Treatment Protocol
AC-T 36 100%

* One participant received a shorter protocol of chemotherapy. Caption: ACT – Cyclophosphamide, Doxorubicin and Docetaxel

There were no differences between the breast cancer patients and matched and health control in terms of age (45.3 years, 44.8 years, and 41.4 years respectively, P>0.05), and FFM (34.2 kg, 36.1 kg and 35.2 kg years respectively, P>0.05). Regarding of weight, BMI, WC and FM, there were also no differences between BC and MC (P>0.05). According to BMI classification and FM results, it was observed a high prevalence of overweight and obesity in the BC group as well as in the MC, and for both measurements (BMI and FM) there were significant differences when both BC and MC were compared to CH (P<0.05). BC females also differed from the MC and HC in terms of PhA and EX/TBW results, in which BC had the lowest values for PhA (5.3). The non-malignancy groups (MC and HC) presented better values of HCS, NRI and BP as well. Table 3 present the complete data of the anthropometric, body composition, nutritional risk, HGS, and blood pressure among the groups.

Table 3: Sample characteristics.

| Variable   | BC (n=36) | MC (n=36) | HC (n=16) | Significance |
|------------|-----------|-----------|-----------|--------------|
|            | Mean  | SD   | Mean  | SD   | Mean  | BC vs MC | BC vs HC | MC vs HC |
| Age (y)    | 45.3  | 8.9  | 44.8  | 9.0  | 41.4  | 9.9  | 0.23     | 0.18     | 0.23     |
| Height (cm)| 159.3 | 7.7  | 162.9 | 5.8  | 161.5 | 7.8  | 0.03     | 0.37     | 0.47     |
| Weight (kg) | 74.0 | 13.8 | 76.6 | 15.3 | 59.8 | 8.2 | 0.1 | **0.03** | **0.01** |
| BMI (kg/m²) | 29.0 | 4.9 | 28.6 | 4.7 | 22.2 | 2.7 | 0.11 | **0.001** | **0.001** |
| WC (cm) | 95.4 | 10.5 | 94.4 | 11.8 | 82.6 | 8.1 | 0.56 | **0.001** | **0.007** |
| FFM (KG) | 34.2 | 9.5 | 36.1 | 6.2 | 35.2 | 7.3 | 0.28 | 0.7 | 0.65 |
| FM (KG) | 28.1 | 9.6 | 30.1 | 11.3 | 18.9 | 4.4 | 0.25 | **0.02** | <0.001 |
| PhA | 5.3 | 0.8 | 6.4 | 0.8 | 6.3 | 0.9 | <0.001 | <0.001 | 0.69 |
| TBW | 33.3 | 7.1 | 33.5 | 4.8 | 30.3 | 7.5 | 0.83 | 0.18 | 0.06 |
| EW | 15.8 | 3.5 | 14.7 | 2.3 | 13.3 | 3.4 | **0.03** | **0.02** | 0.08 |
| IW | 17.5 | 3.9 | 18.5 | 2.7 | 17.0 | 3.7 | 0.17 | 0.7 | 0.12 |
| EW/TBW | 0.5 | 0.0 | 0.4 | 0.0 | 0.4 | 0 | <0.001 | <0.001 | 0.04 |
| BPsys [mmHg] | 122.1 | 16.1 | 115.5 | 13.8 | 111.3 | 10.3 | 0.06 | **0.02** | 0.29 |
| BPdia [mmHg] | 80.7 | 11.6 | 74.3 | 9.0 | 71.1 | 10.5 | **0.02** | **0.008** | 0.28 |
| HGS (kg) | 22.5 | 5.7 | 27.1 | 6.3 | 24.4 | 5.1 | <0.001 | 0.19 | 0.39 |
| NRI | 93.4 | 9.5 | 101.4 | 7.0 | 98.0 | 7.4 | <0.001 | 0.14 | 0.11 |

BC: Breast cancer group, MC: Matched control group, HC: healthy control group, WC: waist circumference, BMI: Body mass index, HGS: Handgrip strength, FFM: Fat-free mass, FM: Fat mass, PhA: Phase angle. TBW: Total body water. EW: Extracellular water. IW: Intracellular water. EX/TW: The ratio between extracellular water and total water BP sys: Systolic blood pressure. BP dia: Diastolic blood pressure. NRI: Nutritional risk index * The mean difference is significant at a level of 0.05.

Considering the nutritional markers tools, BC females had the highest prevalence of inadequacy and critical values for all measurements (PhA; HGS and NRI) when compared with matched and healthy control. MC and HC had no difference in any of those markers. Figure 1 shows those comparisons.

Fig 1a: Prevalence of low handgrip strength; Fig 1b: Prevalence of nutritional risk; Fig 1c: Prevalence of low phase angle values. Captions: BC: Breast cancer patients; MC: Matched control group; HC: Healthy control group. The mean difference is significant at a level of 0.05.

Regarding the food consumption of the groups, daily caloric and carbohydrate intake were higher in the BC group (1744 kcal and 245.2 g respectively) and differ in statistically significance from MC for both values. The range of protein intake/kg for BC group was 0.3 g/kg – 1.9 g/kg, and only 41.6% of the patient (N=15) achieved the minimal recommendation from Espen guidelines. Interesting, BC females also were the group with the highest intake of fiber, being statically
significant when compared to the matched group (P=0.005). Additionally, the other macronutrient distribution did not differ between any participant groups. Table 4 shows the complete food intake results and their comparisons among the groups.

Table 4: Food intake results among the groups.

| Variable         | BC (n=36) | MC (n=36) | HC (n=16) | Significance |
|------------------|-----------|-----------|-----------|--------------|
|                  | Mean      | SD        | Mean      | SD           | Mean        | SD        | BC vs MC | BC vs HC | MC vs HC |
| Energy (kcal)    | 1744.3    | 559.1     | 1363.8    | 572.6        | 1590.2      | 498.0     | 0.004    | 0.35     | 0.19     |
| CHO (g)          | 245.2     | 93.0      | 177.9     | 729.2        | 177.9       | 93.2      | 0.001    | 0.02     | 0.99     |
| Protein (g)      | 77.9      | 24.0      | 72.7      | 39.1         | 78.5        | 25.9      | 0.5      | 0.93     | 0.59     |
| Protein g/kg     | 1.1       | 0.0       | 1.0       | 0.6          | 1.3         | 0.3       | 0.37     | 0.1      | 0.08     |
| Total fat (g)    | 50.7      | 21.0      | 47.3      | 22.3         | 48.5        | 23.1      | 0.51     | 0.74     | 0.86     |
| Col (g)          | 281.5     | 141.7     | 255.3     | 220.0        | 262.1       | 184.9     | 0.99     | 0.69     | 0.83     |
| Fiber (g)        | 15.9      | 7.5       | 10.4      | 6.9          | 13.3        | 7.5       | 0.005    | 0.26     | 0.19     |

Captions: Breast cancer group; MC: Matched control group; HC: healthy control group; CHO: Carbohydrate; Protein g/kg: it was considered the ratio between the total amount of protein and body weight for each participant. Col: Cholesterol. * The mean difference is significant at a level of 0.05.

Concerning about biochemical results, and overall, BC group had the worst value among all analyses, and it was significantly different from the matched group in regarding of FG, TG, HDL, TC, TP, and albumin results (P<0.05). MC and HC did not differ in any biochemical parameters. Table 5 presents the complete data of biochemical test and their variance among the group results.

Table 5: Biochemical test and their variance between the groups.

| Variable | BC (n=36) | MC (n=36) | HC (n=16) | Significance |
|----------|-----------|-----------|-----------|--------------|
|          | Mean      | SD        | Mean      | SD           | Mean        | SD        | BC vs MC | BC vs HC | MC vs HC |
| FG       | 96.6      | 13.4      | 86.2      | 10.6         | 86.7        | 10.2      | 0.02     | 0.11     | 0.88     |
| TG       | 178.3     | 85.7      | 103.4     | 47.3         | 101.6       | 46.9      | <0.001   | 0.001    | 0.9      |
| HDL      | 30.6      | 7.4       | 40.4      | 9.6          | 44.8        | 9.5       | <0.001   | <0.001   | 0.14     |
| LDL      | 94.6      | 21.1      | 86.1      | 19.0         | 80.9        | 21.6      | 0.09     | 0.04     | 0.4      |
| TC       | 160.9     | 27.3      | 147.1     | 23.1         | 146.0       | 26.0      | 0.02     | 0.07     | 0.88     |
|       |      |       |       |       | TP    | CRP   | Albumin |
|-------|------|-------|-------|-------|-------|-------|---------|
|       | 7.5  | 0.9   | 8.2   | 0.8   | 8.5   | 0.7   | <0.001  |
| MC    | 17.8 | 31.8  | 12.1  | 12.9  | 10.6  | 10.3  | 0.4     |
| HG    | 3.4  | 0.6   | 3.9   | 0.5   | 3.7   | 0.5   | <0.001  |
|       |      |       |       |       |       |       |         |
|       |      |       |       |       | 0.22  | 0.46  | 0.67    |
|       |      |       |       |       |       | <0.001|         |
|       |      |       |       |       |       | 0.12  | 0.15    |

Captions: BC: Breast cancer group; MC: Matched control group; HC: healthy control group; FG: Fasting glucose; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC: Total cholesterol; TP: Total protein. CRP: C reactive protein. The mean difference is significant at a level of 0.05.

As expected, following the metabolic differences observed in table 5, BC group patients had worse values of all adiposity markers, for both adiposity index (VAI and LAP), and metabolic and cardiovascular risks measured by TyG index. For the three indices, the mean value of BC group was statistically higher (P<0.05). Furthermore, it was not found difference regarding MC and HC groups for those evaluations. Figure 2 present the distribution of VAI, LAP and TyG among the groups.

Fig 2a: Distribution of visceral fat index; Fig 2b: Distribution of lipid accumulation index; Fig 2c: Distribution of triglyceride glucose index. Captions: BC: Breast cancer patients; MC: Matched control group; HG: Healthy control group. The mean difference is significant at a level of 0.05

**Discussion**

To our knowledge, only a few articles aimed to make similar comparisons. A meta-analysis conducted by Hernandez et al (2014) identified 22 studies in which compared breast cancer patients with a control group. However, only 2 studies included dietetic data besides the metabolic factors comparisons, and we were the only study conducted with Brazilian population in which included both body composition and nutrition status parameters. Breast cancer patients on average are presented with a high prevalence of abdominal obesity, high body weight, BMI and fat mass, and consequently the matched control as well. Both groups differed from the healthy control group in all of those obesity indicators.
The results of our study indicate that, despite similar age, BMI, waist and hip circumferences fat-free mass and fat mass (not statically significant), it was possible to verify impairments in aspects of nutritional status markers among BC and matched control group, but not between the MC and HC groups. BC group presented the lowest values of PhA, and the highest prevalence of low HGS, nutritional risk by NRI and overhydration by EW/TBW. All those parameters are considered indicators of poor nutritional status \(^{8,53–55}\). Regarding PhA, the BC group had values lower than the cutoff proposed by Gupta et al (2008) in which values below 5.6 are considered a sign of poor prognosis for breast cancer patients \(^8\). PhA values for both healthy controls did not differ as well as NRI and HGS values. Besides nutritional status, breast cancer patients on average presented poor indicators of metabolic health, with the highest levels of BP, FG, all lipids’ markers, CRP, and the lowest level of albumin. Despite significant differences in body weight, WC, and fat mass levels, MC and HC did not differ in any biochemical parameters. This result is concordant with previous research that has already reported differences in glucose metabolism and metabolic syndrome prevalence among breast cancer patients \(^{51}\), as well as alterations in insulin homeostasis when compared to the control group \(^{56}\).

Obesity is a condition that is frequently associated with abnormalities in lipid metabolism \(^{57}\), however, in this study, we did not find lipids impairments in the MC group, only among the cancer patients. In addition to body composition, other components can contribute to lipids alterations, as the own tumor, in which lipid metabolism changes influence proliferation and dissemination of cancer cells \(^{58}\), and chemotherapy itself has the potential to promotes modifications in serum lipids \(^{59}\). Thus, those components may explain the reason of presence of lipids alterations only in BC group. Moreover, poor metabolic indicators contribute to increasing the risk of various conditions such as atherosclerosis, and other cardiovascular diseases \(^{24}\), and
according to Bell et al (2014) metabolic syndrome components can increase risk of death by 3 times 51.

In order to verify and compare cardiovascular risk, we included in this study adiposity and lipid accumulation indices. Several studies have already shown the VAI, LAP and TyG indices as simple and good markers of cardiovascular outcomes and as screen tools for cardiovascular disease risk 60–65. Kouli et al (2017), during a 10-year follow-up of a cohort of 3,042 adults, found that VAI was independently associated with an elevated risk of CVD in 10 years 60. Furthermore, considering the TyG index, a study with a Brazilian population found superior performance compared to the HOMA method for estimation of insulin resistance 60. In this study, as expected according to the discrepancies of biochemical blood results among the groups, the BC had the worst value of VAI, LAP and TyG, indicating a visceral fat dysfunction, therefore, high cardiovascular disease risk. Additionally, despite the difference in body composition, it was not found any difference of those indices among the MC and HC.

We attempted to identify possible reasons for the difference in the metabolic and nutritional markers between patients and MC females by measuring food intake as body composition did not influence those results (MC group presented healthier results than BC). There have been many studies performed outlining the role of diet and disturb on glucose and lipids metabolism. A review conducted by Siôn A.P & Hodson L (2017) concluded that energy intake, independent of nutrient content, is a crucial regulator of hepatic lipid accumulation 67. Furthermore, CHO levels in diet are also responsible for metabolic profile alterations where high ingestion is associated with an increase in serum lipids 68,69. Concordantly, in this study, we confirmed breast cancer patients had the highest level of energy and carbohydrate intake, and it was statistically different from the matched group intakes and from HC regarding CHO consumption, however,
considering caloric intakes, it did not differ from the healthy females. We hypothesized that along the reasons we did not find discrepancies in caloric ingestion among patients and the healthy control. There could be differences in the energy expenditure and level of physical activity, notably, and, as a limitation of our study, we did not evaluate those components.

Curiously, BC presented the highest level of fiber ingestion, despite being far from the 25 g/day recommendation, evidencing the diet inadequacies among the population overall. In addition to the dietary shortcomings observed, the patients had low protein intake/kg as well. Although it was not statistically significant when compared to the other groups (MC and HC), it is still clinically relevant, especially considering that changes in nutritional status markers have already been identified in this sample (PhA, NRI and EW/TBW) and low HGS. Besides, there is a potential for the development of sarcopenic obesity in those patients with an intake below 1.2g / kg.

Contrary to our hypotheses, we observed no differences in body composition (FM and FFM) between breast cancer patients and matched females, and also no differences in FFM among the 3 groups, though BC still had a higher nutritional risk. However, as we hypothesized, cancer patients demonstrated impairments in lipids, worst glucose levels, visceral fat dysfunction and consequently higher cardiovascular risk in which those females presented important unhealthy dietary patterns with higher carbohydrate and caloric intake and insufficient protein and fiber ingestion. Accordingly, our findings highlight the need for the implementation of a targeted dietetic approach to treat and mostly to prevent unfavorable metabolic and nutritional outcomes.

Successfully, dietetic management has already shown to be an effective method to control and prevent metabolic impairments; it is particularly important in the breast cancer patient population where the metabolic risks are increased by the tumor and chemotherapy besides the
diet and body composition unfavorable. Remarkably our study has already mentioned-limitations as not inclusion of energy expenditure and physical activity investigation and the sample size was relatively small. For further studies, the inclusion of those components and expanding the follow-up of these patients could better elucidate the mechanism involved in metabolic changes and whether these results are maintained in the long term or enhanced by hormone therapy.

Finally, this study has found that women undergoing breast cancer chemotherapy, after completion of the treatment, presented poor indicators of nutritional and metabolic health, such as PhA, NRI, EW/TBW HGS, dyslipidemia, and visceral fat dysfunction by adiposity indices when compared to a group of age- and BMI-matched non-malignant females. Body composition and age do not explain these differences. Furthermore, the dietetic investigation revealed a higher energy intake and carbohydrate and insufficient consumption of protein and fiber.

Considering the possibility of poor prognosis related to the nutritional markers, sarcopenic obesity or the subsequent threat of developing cardiovascular disease in survivorship, this study highlights the necessity for more effective lifestyle intervention as exercise and nutrition counseling during breast cancer treatment.

Declarations

Funding:

BRS was founded by São Paulo Research Foundation (FAPESP). Grant number: 2017/07963-0 and FAPESP fellowship Grant number: 2019/09877-9. LAPC was founded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES Brasil (Coordination for the Improvement of Higher Education Personnel, in free translation) – Financing Code 001 Doctoral scholarship granted.

Authors' contributions:
The authors’ responsibilities were as follows – AAJJ: conceptualized the study; BRS, LAPC, TOG, and AAJJ: were responsible for the research design; BRS and LAPC: conducted the research and analyzed the data; BRS, MM, and AAJJ: wrote the paper and had primary responsibility for final content; and all authors: contributed to data interpretation and read and approved the final manuscript.

Conflicts of interest/Competing interests:
The authors declare that they have no conflict of interest.

Ethical standard:
All human studies have been approved by the appropriate ethics committee and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.
All persons gave their informed consent prior to their inclusion in the study.

Availability of data and material:
All relevant data are within the paper

Code availability:
Not applicable

Acknowledgments:
We thank all of the research group on Nutrition and Breast Cancer of the University of São Paulo, especially the students who assisted in all phases of the study.
References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021;0(0):1-41. doi:10.3322/caac.21660

2. Institute NC, José Alencar Gomes da Silva (INCA). Estimate/2020 – Cancer Incidence in Brazil. (Institute NCJAG da Silva, ed.); 2019.

3. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). The Lancet. 2015;385(9972):977-1010. doi:https://doi.org/10.1016/S0140-6736(14)62038-9

4. Lee K, Kruper L, Dieli-Conwright CM, Mortimer JE. The Impact of Obesity on Breast Cancer Diagnosis and Treatment. Current Oncology Reports. 2019;21(5). doi:10.1007/s11912-019-0787-1

5. Irwin ML, McTiernan A, Baumgartner RN, et al. Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(4):774-782. doi:10.1200/JCO.2005.04.036

6. Caan BJ, Cespedes Feliciano EM, Prado CM, et al. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. JAMA Oncology. 2018;4(6):798-804. doi:10.1001/jamaoncol.2018.0137

7. Marques VA, Ferreira-Junior JB, Lemos T V., et al. Effects of chemotherapy treatment on muscle strength, quality of life, fatigue, and anxiety in women with breast cancer. International Journal of Environmental Research and Public Health. 2020;17(19):1-10. doi:10.3390/ijerph17197289

8. Gupta D, Lammersfeld CA, Vashi PG, King J, Dahlk SL, Grutsch JF. Bioelectrical impedance phase angle as a prognostic indicator in breast cancer. BMC Cancer. 2008;8:1-7. doi:10.1186/1471-2407-8-249

9. Pagano AP, Sicchieri JMF, Schiavoni IL, et al. Phase angle as a severity indicator for liver diseases. Nutrition. 2020;70. doi:10.1016/j.nut.2019.110607

10. Hui D, Dev R, Pimental L, et al. Association Between Multi-frequency Phase Angle and Survival in Patients With Advanced Cancer. Journal of pain and symptom management. 2017;53(3):571-577. doi:10.1016/j.jpainsymman.2016.09.016

11. da Silva BR, Gonzalez MC, Cereda E, Prado CM. Exploring the potential role of phase angle as a marker of oxidative stress: a narrative review. Nutrition. Published online 2021:111493. doi:https://doi.org/10.1016/j.nut.2021.111493

12. Ramos da Silva B, Mialich MS, Cruz LP, Rufato S, Gozzo T, Jordao AA. Performance of functionality measures and phase angle in women exposed to chemotherapy for early breast cancer. Clinical Nutrition ESPEN. Published online 2021. doi:https://doi.org/10.1016/j.clnesp.2021.02.007

13. Carolina J, Godinho-mota M, Felipe J, et al. Chemotherapy negatively impacts body composition, physical function and metabolic profile in patients with breast cancer. Clinical Nutrition. 2022;(xxxx). doi:10.1016/j.clnu.2020.11.020
14. Ramos da Silva B, Rufato S, Mialich MS, Cruz LP, Gozzo T, Jordao AA. Metabolic Syndrome and unfavorable outcomes on body composition and in visceral adiposities indexes among early breast cancer women post-chemotherapy. *Clinical Nutrition ESPEN*. Published online 2021. doi:https://doi.org/10.1016/j.clnesp.2021.06.001

15. Godinho-Mota JCM, Mota JF, Gonçalves LV, et al. Chemotherapy negatively impacts body composition, physical function and metabolic profile in patients with breast cancer. *Clinical Nutrition*. Published online 2020. doi:https://doi.org/10.1016/j.clnu.2020.11.020

16. Bagyura Z, Kiss L, Lux Á, et al. Association between coronary atherosclerosis and visceral adiposity index. *Nutrition, metabolism, and cardiovascular diseases : NMCD*. 2020;30(5):796-803. doi:10.1016/j.numecd.2020.01.013

17. Demirbas N, Kutlu R. Importance of Measured Body Fat, Visceral Adiposity Index, and Lipid Accumulation Product Index in Predicting Cardiometabolic Risk Factors. *Metabolic syndrome and related disorders*. Published online October 2020. doi:10.1089/met.2020.0098

18. Cheng YL, Wang YJ, Lan KH, et al. Fatty Liver Index and Lipid Accumulation Product Can Predict Metabolic Syndrome in Subjects without Fatty Liver Disease. Uchiyama K, ed. *Gastroenterology Research and Practice*. 2017;2017:9279836. doi:10.1155/2017/9279836

19. Cartolano FDC, Pappiani C, Freitas MCP de, Figueiredo Neto AM, Carioca AAF, Damasceno NRT. Is Lipid Accumulation Product Associated with an Atherogenic Lipoprotein Profile in Brazilian Subjects? *Arquivos brasileiros de cardiologia*. 2018;110(4):339-347. doi:10.5935/abc.20180054

20. Cardoso-Peña E, Soto Pina AE, Villanueva ÁG, et al. Visceral Adiposity Index in Breast Cancer Survivors: A Case-Control Study. *International journal of endocrinology*. 2020;2020:8874916. doi:10.1155/2020/8874916

21. Mialich MS, Silva BR, Cruz LAP da, Almeida AM de, Gozzo T de O, Jordao AA. Assessment of the nutritional and metabolic profile of women with breast cancer and its association with metabolic syndrome. *Journal of Nutrition and Intermediary Metabolism*. 2018;12(June):14-19. doi:10.1016/j.jnim.2018.05.004

22. Amaral P, Miguel R, Mehdad A, et al. Body fat and poor diet in breast cancer women. *Nutricion Hospitalaria*. 2010;25(3):456-461. doi:10.3305/nh.2010.25.3.4418

23. Buttros DDAB, Branco MT, Orsatti CL, Almeida-Filho BDS, Nahas-Neto J, Nahas EAP. High risk for cardiovascular disease in postmenopausal breast cancer survivors. *Menopause*. 2019;26(9):1024-1030. doi:10.1097/GME.0000000000001348

24. Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. *Translational research : the journal of laboratory and clinical medicine*. 2017;183:57-70. doi:10.1016/j.trsl.2017.01.001

25. Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of non-communicable disease: Implications for research and public health. *Environmental Health: A Global Access Science Source*. 2012;11(1):1-9. doi:10.1186/1476-069X-11-42

26. Haffner S, Taegtmeyer H. Epidemic obesity and the metabolic syndrome. *Circulation*. 2003;108(13):1541-1545. doi:10.1161/01.CIR.0000088845.17586.EC
27. La Vecchia C, Negri E, Franceschi S, et al. Body mass index and post-menopausal breast cancer: an age-specific analysis. *British journal of cancer*. 1997;75(3):441-444. doi:10.1038/bjc.1997.73

28. Redig AJ, Munshi HC. Care of the cancer survivor: metabolic syndrome after hormone-modifying therapy. *The American journal of medicine*. 2010;123(1):87.e1-87.e876. doi:10.1016/j.amjmed.2009.06.022

29. Lohman TG., et al. (1988): Anthropometric Standardization Reference Manual. Human. 1940-Roche, Alex F. 1921. Accessed May 6, 2020. http://www.scielo.com/reference/226305

30. WHO/Europe | Nutrition - Body mass index - BMI. Accessed May 6, 2020. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi

31. Nishikawa H, Yoh K, Enomoto H, et al. Extracellular Water to Total Body Water Ratio in Viral Liver Diseases: A Study Using Bioimpedance Analysis. *Nutrients*. 2018;10(8). doi:10.3390/nu10081072

32. Fess E. *Clinical Assessment Recommendations | American Society of Hand Therapists (ASHT)*; 1992.

33. Luna-Heredia E, Martín-Peña G, Ruiz-Galiana J. Handgrip dynamometry in healthy adults. *Clinical Nutrition*. 2005;24(2):250-258. doi:10.1016/j.clnu.2004.10.007

34. Bielemann RM, Gigante DP, Horta BL. Birth weight, intrauterine growth restriction and nutritional status in childhood in relation to grip strength in adults: from the 1982 Pelotas (Brazil) birth cohort. *Nutrition (Burbank, Los Angeles County, Calif)*. 2016;32(2):228-235. doi:10.1016/j.nut.2015.08.014

35. Nightingale H, Walsh KJ, Olupot-Olupot P, et al. Validation of triple pass 24-hour dietary recall in Ugandan children by simultaneous weighed food assessment. *BMC nutrition*. 2016;2:56. doi:10.1186/s40795-016-0092-4

36. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clinical Nutrition*. 2017;36(1):11-48. doi:10.1016/j.clnu.2016.07.015

37. Korczak R, Slavin JL. Definitions, regulations, and new frontiers for dietary fiber and whole grains. *Nutrition Reviews*. 2020;78(Supplement_1):6-12. doi:10.1093/nutrit/nuz061

38. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry*. 1972;18(6):499-502. doi:10.1093/clinchem/18.6.499

39. Buzby GP, Knox LS, Crosby LO, et al. Study protocol: A randomized clinical trial of total parenteral nutrition in malnourished surgical patients. *American Journal of Clinical Nutrition*. 1988;47(2 SUPPL.):366-381. doi:10.1093/ajcn/47.2.366

40. Bouillanne O, Morineau G, Dupant C, et al. Geriatric Nutritional Risk Index: A new index for evaluating at-risk elderly medical patients. *American Journal of Clinical Nutrition*. 2005;82(4):777-783. doi:10.1093/ajcn/82.4.777

41. Nahler G, Nahler G. Lorentz-formula. In: *Dictionary of Pharmaceutical Medicine*. Springer Vienna; 2009:107-107. doi:10.1007/978-3-211-89836-9_803

42. Aziz EF, Javed F, Pratap B, et al. Malnutrition as assessed by nutritional risk index is associated with worse outcome in patients admitted with acute decompensated heart
failure: An ACAP-HF data analysis. *Heart International*. 2011;6(1):3-8. doi:10.4081/hi.2011.e2

43. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metabolic syndrome and related disorders*. 2008;6(4):299-304. doi:10.1089/met.2008.0034

44. Amato MC, Giordano C, Galia M, et al. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes care*. 2010;33(4):920-922. doi:10.2337/dc09-1825

45. Kahn HS. The “lipid accumulation product” performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. *BMC Cardiovascular Disorders*. 2005;5(1):26. doi:10.1186/1471-2261-5-26

46. de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifai N. Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. *Circulation*. 2004;110(16):2494-2497. doi:10.1161/01.CIR.0000145117.40114.C7

47. Dong H, Xu Y, Zhang X, Tian S. Visceral adiposity index is strongly associated with hyperuricemia independently of metabolic health and obesity phenotypes. *Scientific Reports*. 2017;7(1):8822. doi:10.1038/s41598-017-09455-z

48. Ahn N, Baumeister SE, Amann U, et al. Visceral adiposity index (VAI), lipid accumulation product (LAP), and product of triglycerides and glucose (TyG) to discriminate prediabetes and diabetes. *Scientific Reports*. 2019;9(1):9693. doi:10.1038/s41598-019-46187-8

49. Li X, Liu ZL, Wu YT, et al. Status of lipid and lipoprotein in female breast cancer patients at initial diagnosis and during chemotherapy. *Lipids in Health and Disease*. 2018;17(1):1-6. doi:10.1186/s12944-018-0745-1

50. Hernandez A V., Guarnizo M, Miranda Y, et al. Association between insulin resistance and breast carcinoma: A systematic review and meta-analysis. *PLoS ONE*. 2014;9(6). doi:10.1371/journal.pone.0099317

51. Bell KE, Di Sebastiano KM, Vance V, et al. A comprehensive metabolic evaluation reveals impaired glucose metabolism and dyslipidemia in breast cancer patients early in the disease trajectory. *Clinical nutrition (Edinburgh, Scotland)*. 2014;33(3):550-557. doi:10.1016/j.clnu.2013.08.001

52. Fair AM, Dai Q, Shu XO, et al. Energy balance, insulin resistance biomarkers, and breast cancer risk. *Cancer detection and prevention*. 2007;31(3):214-219. doi:10.1016/j.cdp.2007.04.003

53. Tanaka S, Ando K, Kobayashi K, et al. Higher extracellular water-to-total body water ratio more strongly reflects the locomotive syndrome risk and frailty than sarcopenia. *Archives of gerontology and geriatrics*. 2020;88:104042. doi:10.1016/j.archger.2020.104042

54. Ferreira A, Gonçalves I, Moreira G, et al. P1.07-06 Use of the Nutritional Risk Index as Screening for Malnutrition in Patients with Lung Cancer. *Journal of Thoracic Oncology*. 2019;14(10):S489. doi:10.1016/j.jtho.2019.08.1015

55. Yoshimura da Costa T, Yukari Suganuma J, Faria S de, Bernardes Spexoto MC. Association of adductor pollicis muscle thickness and handgrip strength with nutritional status in...
56. Luque RM, López-Sánchez LM, Villa-Osaba A, et al. Breast cancer is associated to impaired glucose/insulin homeostasis in premenopausal obese/overweight patients. *Oncotarget*. 2017;8(46):81462-81474. doi:10.18632/oncotarget.20399

57. Kojta I, Chacińska M, Blachnio-Zabielska A. Obesity, Bioactive Lipids, and Adipose Tissue Inflammation in Insulin Resistance. *Nutrients*. 2020;12(5). doi:10.3390/nu12051305

58. Fernández LP, de Cedrón M, de Molina A. Alterations of Lipid Metabolism in Cancer: Implications in Prognosis and Treatment. *Frontiers in Oncology*. 2020;10:2144. doi:10.3389/fonc.2020.577420

59. He T, Wang C, Tan Q, et al. Adjuvant chemotherapy-associated lipid changes in breast cancer patients: A real-word retrospective analysis. *Medicine*. 2020;99(33).

60. Kouli GM, Panagiotakos DB, Kyrou I, et al. Visceral adiposity index and 10-year cardiovascular disease incidence: The ATTICA study. *Nutrition, metabolism, and cardiovascular diseases : NMCD*. 2017;27(10):881-889. doi:10.1016/j.numecd.2017.06.015

61. Jin JL, Cao YX, Wu LG, et al. Triglyceride glucose index for predicting cardiovascular outcomes in patients with coronary artery disease. *Journal of thoracic disease*. 2018;10(11):6137-6146. doi:10.21037/jtd.2018.10.79

62. Costa EC, Sá JCF de, Soares EMM, Lemos TMAM, Maranhão TM de O, Azevedo GD. [Evaluation of cardiovascular risk by the LAP index in non-obese patients with polycystic ovary syndrome]. *Arquivos brasileiros de endocrinologia e metabologia*. 2010;54(7):630-635. doi:10.1590/s0004-273020100001000007

63. Amato MC, Giordano C. Visceral adiposity index: an indicator of adipose tissue dysfunction. *International journal of endocrinology*. 2014;2014:730827. doi:10.1155/2014/730827

64. Scanferla F, Landini S, Fracasso A, et al. On-Line Bioelectric Impedance During Haemodialysis: Monitoring of Body Fluids and Cell Membrane Status. *Nephrology Dialysis Transplantation*. 1990;5(suppl 1):167-170. doi:10.1093/ndt/5.suppl_1.167

65. Adu EA, Obirikorang C, Acheampong E, et al. Lipid accumulation product (LAP) index as a potential risk assessment for cardiovascular risk stratification among type II diabetes mellitus in a Ghanaian population: A cross-sectional study. Ndisang JF, ed. *Cogent Medicine*. 2019;6(1):1639880. doi:10.1080/2331205X.2019.1639880

66. Vasques ACJ, Novaes FS, de Oliveira M da S, et al. TyG index performs better than HOMA in a Brazilian population: A hyperglycemic clamp validated study. *Diabetes Research and Clinical Practice*. 2011;93(3):e98-e100. doi:https://doi.org/10.1016/j.diabres.2011.05.030

67. Parry SA, Hodson L. Influence of dietary macronutrients on liver fat accumulation and metabolism. *Journal of Investigative Medicine*. 2017;65(8):1102 LP - 1115. doi:10.1136/jim-2017-000524

68. Lee HA, An H. The Effect of High Carbohydrate-to-fat Intake Ratios on Hypo-HDL-cholesterolemia Risk and HDL-cholesterol Levels over a 12-year Follow-up. *Scientific Reports*. 2020;10(1):913. doi:10.1038/s41598-020-57931-w
69. Ma Y, Li Y, Chiriboga DE, et al. Association between carbohydrate intake and serum lipids. *Journal of the American College of Nutrition*. 2006;25(2):155-163. doi:10.1080/07315724.2006.10719527

70. Limon-Miro AT, Lopez-Teros V, Astiazaran-Garcia H. Dietary Guidelines for Breast Cancer Patients: A Critical Review. *Advances in nutrition (Bethesda, Md)*. 2017;8(4):613-623. doi:10.3945/an.116.014423

71. Pérez EA, González MP, Martínez-Espinosa RM, Vila MDM, Reig García-Galbis M. Practical Guidance for Interventions in Adults with Metabolic Syndrome: Diet and Exercise vs. Changes in Body Composition. *International journal of environmental research and public health*. 2019;16(18):3481. doi:10.3390/ijerph16183481

72. Pérez-Martínez P, Mikhailidis DP, Athyros VG, et al. Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation. *Nutrition reviews*. 2017;75(5):307-326. doi:10.1093/nutrit/nux014

73. Santiago-Torres M, Shi Z, Tinker LF, et al. Diet quality indices and risk of metabolic syndrome among postmenopausal women of Mexican ethnic descent in the Women’s Health Initiative Observational Study. *Nutrition and healthy aging*. 2020;5(4):261-272. doi:10.3233/NHA-190076

74. Di Daniele N, Noce A, Vidiri MF, et al. Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. *Oncotarget*. 2017;8(5):8947-8979. doi:10.18632/oncotarget.13553
Lipid accumulation product (LAP)

P < 0.001

P = 0.18

BC, MC, HC
