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Trabajo Original

Obesidad y síndrome metabólico

Visceral adiposity increases the risk of breast cancer: a case-control study

La adiposidad visceral aumenta el riesgo de cáncer de mama: un estudio de casos y controles

Jordana Carolina Marques Godinho-Mota[1], Karine Anusca Martins[1], Larissa Vaz-Gonçalves[1], João Felipe Mota[2], Leonardo Ribeiro Soares[1] and Ruffo Freitas-Junior[1]

[1]Program of Mastology. Federal University of Goiás. Goiania, Brazil. [2]Clinical and Sports Nutrition Research Laboratory (Labince). Faculty of Nutrition. Federal University of Goiás. Goiania, Brazil

Abstract

Introduction: in recent decades, lifestyle changes in women involving physical inactivity, insulin resistance and body fat distribution have been associated with an increase in breast cancer.

Objective: to assess whether insulin resistance, lipid profile, and visceral adiposity are associated with increased risk of breast cancer.

Methods: a hospital-based case control study was conducted with 116 women newly diagnosed with breast cancer and 226 controls. Body mass index, waist circumference, total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), very-low-density lipoproteins (VLDL), triglycerides, glycated hemoglobin, HOMA-IR, HOMA-β, lipid accumulation product (LAP), and visceral adiposity index (VAI) were assessed. Logistic regression was adjusted for body mass index and age to quantify the association between breast cancer risk and insulin resistance, dyslipidemias, and visceral adiposity.

Key words:

Breast cancer. Insulin resistance. Visceral adiposity. Lipid profile.

Results: the case group had higher insulin resistance ($p < 0.001$), LAP ($p = 0.012$), and VAI ($p = 0.004$), and lower concentrations of HDL ($p = 0.024$) and HOMA-β ($p = 0.010$) compared to the control. Insulin resistance (OR = 3.00, 95% CI: 1.75-5.17, $p < 0.001$) and higher VAI (OR = 1.91, 95% CI: 1.17-3.13, $p = 0.01$) were associated with breast cancer, whereas the highest concentration of HDL reduces the chances of cancer by 53% (95% CI: 0.32-0.86, $p = 0.026$). In the multivariate analysis, only LAP and VAI were associated to breast cancer.

Conclusions: visceral fat accumulation increases the risk of breast cancer.

Resumen

Introducción: en las últimas décadas, los cambios de estilo de vida en las mujeres relacionados con la actividad física, la resistencia a la insulina y la distribución de la grasa corporal se han asociado con el aumento de cáncer de mama.

Objetivo: evaluar si la resistencia a la insulina, el perfil lipídico y la adiposidad visceral están asociados con un mayor riesgo de padecer cáncer de mama.

Métodos: se realizó un estudio de casos y controles en hospitales en el que participaron 116 mujeres recién diagnosticadas con cáncer de mama y 226 controles. Fueron evaluados índice de masa corporal, circunferencia de la cintura, colesterol total, lipoproteínas de alta densidad (HDL), lipoproteínas de baja intensidad (LDL), lipoproteínas de muy baja densidad (VLDL), triglicéridos, hemoglobina glicosilada, HOMA-IR, HOMA-β, el producto de acumulación de líquidos (LAP) y el índice de adiposidad visceral (VAI). La regresión logística se adaptó al índice de masa corporal y a la edad para cuantificar la asociación entre el riesgo de cáncer de mama y la resistencia a la insulina, dislipidemias y adiposidad visceral.

Palabras clave:

Cáncer de mama. Resistencia a la insulina. Adiposidad visceral. Perfil lipídico.

Resultados: el grupo de casos presentó mayor resistencia a la insulina ($p < 0,001$), LAP ($p = 0,012$) y VAI ($p = 0,004$) y menores concentraciones de HDL ($p = 0,024$) y HOMA-β ($p = 0,010$) frente al grupo de control. La resistencia a la insulina (OR = 3,00, IC 95%: 1,75-5,17, $p < 0,001$) y mayor VAI (OR = 1,91, IC 95%: 1,17-3,13, $p = 0,01$) fueron asociadas al cáncer de mama, mientras que la mayor concentración de HDL reduce las probabilidades de cáncer al 53% (IC 95%: 0,32-0,86, $p = 0,026$). En el análisis multivariado, solo LAP y VAI se asociaron al cáncer de mama.

Conclusión: la acumulación de grasa visceral aumenta el riesgo de cáncer de mama.

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Informed consent: The study was approved by the Human Research Ethics Committee of the Federal University of Goiás (reference number 751.387/2014). Participants were informed of the risks and purposes of the study before written consent was obtained. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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Correspondence:

Jordana Carolina Marques Godinho-Mota. Faculty of Nutrition. Federal University of Goiás. St. 227, block 68. Setor Leste Universitário. 74.605-080, Goiania, Brazil

e-mail: jordana.godinho@hotmail.com

INTRODUCTION

In Brazil, breast cancer is one of the most common types of cancer and the leading cause of cancer mortality in women (1). According to estimates from the American Institute for Cancer Research (AICR), in the next 14 years the prevalence of breast cancer in Brazilian women is expected to increase by 1.8 times, with an estimated 104,617 new cases in 2030 (2).

In recent decades, several factors of modifiable or potentially modifiable risks have been associated with mammary carcinogenesis, such as physical inactivity, body adiposity, and body fat distribution (3,4). However, there is no consensus on the link between adiposity and breast cancer, since there is no differentiation between the total body fat mass and its distribution in some of these studies (3,4-9).

Insulin resistance and lipid abnormalities resulting from the accumulation of body fat are risk factors for well-established cardiovascular disease (7,8). However, the combination of these changes with breast cancer remains unknown and, recently, some studies have suggested an association among increased triglyceride (TG) concentrations, low density lipoproteins (LDL), and decreased high density lipoprotein (HDL) concentrations in the pathogenesis of some types of cancer, especially breast cancer (9,10).

Insulin sensitivity seems to have a key role in the risk of breast cancer, since obese women without insulin resistance have significantly less risk (11). This raises the hypothesis that the concentration of fat in the abdominal region as well as lipid levels and insulin resistance may increase the risk of breast cancer.

MATERIALS AND METHODS

STUDY DESIGN

This is a case-control study conducted in a university hospital of reference for diagnosis and treatment of breast cancer, with the data collected in the period between August 2014 and June 2016.

PARTICIPANTS AND CALCULATION OF THE SAMPLE

The study included women aged between 30 and 80 years. In the case group, those with a recent breast cancer diagnosis (incident case), immediately after diagnostic confirmation by biopsy and before the start of any treatment were considered as eligible, and those who had metastasis, recurrence, or history of another cancer were excluded. The control group included women without a history of breast cancer or other anatomical sites who recently underwent mammography and physical examination of the breasts without changes.

Exclusion criteria included the presence of any cognitive or psychiatric impairment that prevented the understanding of the work and the collection of necessary information. The carriers of clinical conditions that compromised nutritional status and/or damage to physical activities, such as diabetes mellitus, hypothyroidism, metabolic syndrome, morbid obesity, hypercholesterolemia, and hypertriglyceridemia were also excluded (12). The two groups were matched for age (five years) and nutritional status, which was initially classified using the body mass index (BMI).

To calculate the sample size, an expected prevalence of insulin resistance measured by HOMA-IR of 34.0% was considered in women without cancer and 52.6% for those newly diagnosed with breast cancer (13). A significance level of 5.0% was admitted, considering a two-tailed test, a rejection power of the null hypothesis of 90.0%, and a composition of two controls for each case. The estimated minimum necessary sample was 110 cases and 220 controls, totaling 330 women in the study.

ANTHROPOMETRIC AND BIOCHEMICAL PARAMETERS

We conducted a pilot study for the adequacy, accuracy, and precision of anthropometric measurements and body composition using as a reference the anthropometry standardization technique recommended by Habicht (1974) (14).

We used a digital anthropometric scale, with an accuracy of 0.1 kg and a 150 kg capacity, for the evaluation of body weight (kg), and a stadiometer, with an accuracy of 0.1 cm, to obtain height. Both were performed with the procedures described by Heyward and Stolarczyk (2000) (15). BMI was calculated by the ratio of weight (kg) by the square of height (m). We used the cut-off points recommended by the World Health Organization (WHO) (1997) (16). Waist circumference (WC) was measured in triplicate with inextensible and inelastic millimeter tape with accuracy of 0.1 cm at the midpoint between the anterior superior iliac crest and the last rib (17).

To evaluate the glycemic and lipid profile, peripheral vein blood samples were collected in the morning after 12 hours of fasting, 24 hours in the absence of strenuous effort, and 72 hours without drinking alcohol. The plasma samples were separated from the whole blood by centrifugation at 3,500 rpm for ten minutes at 4 °C (Combate, C.E.L.M).

The total cholesterol (TC), HDL, TG, and fasting plasma glucose (FPG) were determined by enzymatic colorimetric method using an automatic analyzer System Vitros® Chemistry 950 Xrl (Johnson & Johnson). The concentration of LDL was calculated using the Friedewald formula for TG values up to 400 mg/dl, where LDL = CT-HDL-TG/5 (18). The determination of glycated hemoglobin was performed by automated equipment turbidimetric method A-25 Biosystems®. The insulin was determined using Insulin AccuBind ELISA kits (Monobind Inc.©). The CV% of the assay corresponding to insulin was CV% = 5.1 intra-assay and 7.2 inter-assay. HOMA-IR and HOMA-β were calculated to evaluate the insulin resistance and functional capacity of pancreatic beta cells, respectively (19). Patients who had values greater than 2.7 were classified as insulin-resistant (20).

The visceral adiposity index (VAI) and the lipid accumulation product (LAP) were obtained by the respective formulas:

VAI = WC/(36.58 + 1.89 x BMI) x (TG/0.81) x (1.52/HDL) (6); LAP = (WC [cm] - 58 x TG concentration [mmol/l]) (5).

In order to ensure good reliability of the results obtained in the measurement of visceral adiposity, patients who had TG levels higher than 279 mg/dl, morbid obesity (BMI 39.99 kg/m²), and pendulous abdomen were excluded from these analyses (6). The VAI, LAP, and HOMA-β values were categorized according to the distribution of the total sample in less than or equal to the 50th percentile and above the 50th percentile. This distribution was adopted because there are no validated cut-off points for these indexes in a sample diagnosed with breast cancer.

STATISTICS

The database was entered in duplicate in the Epi-Info™ (version 7.1.5) and data analysis in Stata software for Windows (version 12.0), considering diagnosis of breast cancer as the outcome variable. We used the Kolmogorov-Smirnov test to verify the normal distribution of continuous variables. To compare continuous variables between groups, the Mann-Whitney U test was applied (non-parametric distribution). Posteriorly, a binary logistic regression adjusted by age and BMI, respectively, was performed in order to get the odds ratio (OR) and 95% confidence interval (95% CI). The coefficient of determination (R^2) was evaluated for diagnosis by the regression model. In addition, collinearity between the variables was tested by correlation test and none returned significant values ($r > 0.90$) that excluded them from the logistic regression analysis. Variables whose significance level was less than 0.05 ($a < 5.0\%$) were considered to be associated with breast cancer outcome. Backward stepwise regression was used to determine independent covariates contributing to the final model on multivariate analysis.

RESULTS

The study included 342 women, 116 newly diagnosed with breast cancer and 226 healthy, with a mean age of 52.36 ± 11.05 years. The majority (61.11%) was in post-menopause, and the average age of menopause did not differ between groups (cases: 46.82 ± 6.41 years; controls: 47.61 ± 6.52 years; p = 0.400). There was a prevalence of overweight patients (67.84%, n = 232) in both groups, with an average BMI of 27.26 ± 4.87 kg/m² and 26.68 ± 5.06 kg/m² between cases and controls, respectively (p = 0.929).

Among the glycemic profile variables, only glycated hemoglobin showed no mean differences between groups. Additionally, women newly diagnosed with breast cancer had higher VAI and LAP and lower HDL when compared to controls (Table I).

It was observed that there was a higher prevalence of women in the case group with fasting insulin above the 50th percentile when compared to healthy women (OR = 2.87, 95% CI: 1.70-4.85). Similar results were found for the categories of glucose intolerance, as measured by fasting glucose (OR = 2.11, 95% CI: 1.21-3.69) and insulin resistance (OR = 3.00, 95% CI: 1.75-5.17). VAI and LAP above the 50th percentile increased by 91% and 74% the chances of having breast cancer (OR = 1.91, 95% CI: 1.17-3.13 and OR = 1.74, 95% CI: 1.06-2.85), respectively. In contrast, HDL above 50 mg/dl reduced the chances for breast cancer by 53% (Table II). On multivariate analysis using (Table III), we found that VAI and LAP were associated with breast cancer.

Table I. Differences in glycemic and lipid profile and markers of abdominal fat between cases and controls

Variables	Controls (n = 226)		Cases (n = 116)		p*
	Median	Interquartile	Median	Interquartile	
Fasting glucose (mg/dl)	89.0	83.0-95.0	93.0	86.0-101.0	*0.004*
Hemoglobin A1C (%)	6.0	5.3-6.9	5.9	5.4-6.9	0.652
Insulin (uU/ml)	7.7	5.5-10.9	9.9	7.0-14.2	*< 0.001*
HOMA-IR	1.8	1.2-2.6	2.3	1.6-3.6	*< 0.001*
HOMA-β	106.8	79.6-153.6	122.4	92.0-190.9	*0.010*
Total cholesterol (mg/dl)	193.0	166.0-217.0	196.0	170.0-216.0	0.750
HDL (mg/dl)	56.0	48.0-66.0	52.0	44.0-61.0	*0.024*
LDL (mg/dl)	113.5	88.5-133.0	115.0	90.0-137.5	0.383
VLDL (mg/dl)	21.0	15.0-31.0	23.0	17.5-30.5	0.106
Triglycerides (mg/dl)	106.0	77.0-154.0	118.0	90.0-153.0	0.123
Visceral adiposity index	1.6	1.0-2.5	1.95	1.3-2.8	*0.004*
Lipid accumulation product	23.1	17.1-32.7	27.2	18.5-38.0	*0.012*

**Mann-Whitney U test. HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein.*

Table II. Association of insulin resistance, lipid profile, markers of abdominal fat and breast cancer risk in women

Variables	Controls (n = 226)		Cases (n = 116)		β (constant)	OR (95% CI)	p*
	n	%	n	%			
Fasting glucose (mg/dl)							
< 100	183	82.4	75	70.8	0.70 (-0.56)	1.00	*0.009*
100-125	39	17.6	31	29.2		2.11 (1.21-3.69)	
Hemoglobin A1C							
< 6.50	141	64.0	68	64.8	-0.03	1.00	*0.906*
≥ 6.50	79	35.1	37	35.2	(-0.91)	0.97 (0.59-1.58)	
Insulin (uU/ml)							
< 8.51	122	57.3	37	35.9	0.94	1.00	*< 0.001*
≥ 8.51	91	42.7	66	64.1	(0.73)	2.87 (1.70-4.85)	
Homa-IR							
< 2.71	166	77.9	60	58.2	1.01	1.00	*< 0.001*
≥ 2.71	47	22.1	43	41.8	(-0.39)	3.00 (1.75-5.17)	
Homa-β							
< 113.16	112	52.6	46	44.7	0.31	1.00	*0.112*
≥ 113.16	101	47.4	57	55.3	(-1.18)	1.49 (0.91-2.44)	
Total cholesterol (mg/dl)							
< 200	128	56.9	68	60.2	-0.14	1.00	*0.492*
≥ 200	97	43.1	45	39.8	(-1.00)	0.85 (0.53-1.36)	
HDL (mg/dl)							
< 51	68	30.2	48	42.5	-0.55	1.00	*0.011*
≥ 51	157	69.8	65	57.5	(0.31)	0.53 (0.32-0.86)	
LDL (mg/dl)							
< 130	160	71.4	73	65.2	0.30	1.00	*0.256*
≥ 130	64	28.6	39	34.8	(-1.02)	1.33 (0.81-2.19)	
VLDL (mg/dl)							
< 23	125	56.0	52	46.4	0.38	1.00	*0.066*
≥ 23	98	44.0	60	53.6	(-1.02)	1.55 (0.97-2.49)	
Triglycerides (mg/dl)							
< 150	164	72.9	82	72.6	-0.01	1.00	*0.840*
≥ 150	61	27.1	31	27.4	(-1.02)	1.05 (0.63-1.76)	
Visceral adiposity index							
< 1.72	120	55.3	44	41.5	0.59	1.00	*0.010*
≥ 1.72	97	44.7	62	58.5	(-6.98)	1.91 (1.17-3.13)	
Lipid accumulation product							
< 24.39	117	53.9	45	42.4	0.49	1.00	*0.027*
≥ 24.39	100	46.1	61	57.5	(-0.82)	1.74 (1.06-2.85)	

**Logistic regression adjusted for age and BMI. β: beta coefficients; HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein; OR: odds ratio.*

DISCUSSION

The main finding in this study was the association of the visceral adiposity to the outcome. Furthermore, values above 50 mg/dl HDL were inversely related to breast cancer in the univariate analysis. It is noteworthy that the VAI and the LAP are representative indicators of a higher risk for the development of and mortality from heart disease, diabetes, and hypertension in different pop-

Table III. Multivariate regression analysis of risk factors for breast cancer

Variables	β	OR (95% CI)	p*
Visceral adiposity index			
< 1.72		1.00	
≥ 1.72	0.72	1.98 (1.19-3.29)	0.008
Lipid accumulation product			
< 24.39		1.00	
≥ 24.39	0.64	1.80 (1.09-3.01)	0.023

*Constant: -1.30. *Backward logistic regression. β: beta coefficients; HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein; OR: odds ratio.*

ulations (5-8). However, we did not identify other studies investigating their association with breast cancer.

Adipose tissue is an endocrine organ composed mainly of subcutaneous adipose tissue (SAT), located in the hypodermis, and visceral adipose tissue (VAT), which is in the deepest layer of the abdomen, around the organs. There has been observed an increase in VAT in sedentary people, as well as in the aging process, especially after menopause, due to hormonal changes (21). Adipose tissue is directly related to an increased risk of cardiovascular and metabolic diseases; however, its association with the pathophysiology of breast cancer is still uncertain (5-8,21-23).

In the current study, there was a positive association between breast cancer and the VAI and LAP indexes for the assessment of VAT. This association may be due to chronic systemic inflammation due to increased production of pro-inflammatory cytokines, such as C-reactive protein, tumor necrosis factor (TNF-α), and interleukin-6 (IL-6) via toll-like receptor 4 (TLR4) activation and the production of reactive oxygen species (21-26). Moreover, visceral adiposity may result in adipocyte hypertrophy, increased lipolytic activity, and insulin resistance, which results in compensatory hyperinsulinemia (9-11).

Adipocytes in the android region increase the availability of free estrogen through androgen hormone conversion by the enzyme aromatase (9). Thus, it is an important risk factor for breast cancer for possessing an anti-apoptotic and pro-angiogenic effect and an inducer of cell proliferation by binding to the estrogen receptor (ER) in breast cells (10). Some studies have noted increased local secretion of cortisol and pro-inflammatory adipokines, which may also be a cause for increased risk of proliferative diseases such as breast cancer (9-11,21-26).

These mechanisms may explain the association between breast cancer and higher VAI values. The use of this index in clinical practice may help to identify patients at higher risk of developing breast cancer and be useful in the monitoring of women with a previous diagnosis without increasing the costs to health, since they are derived from tests and routine measures that are usually used in the care of women on an outpatient basis.

The association between abnormal glucose and insulin resistance and mammary carcinogenesis remains unclear. However, several studies have found results similar to those observed in this study (9-11,24,27,28), mainly related to insulin resistance.

Insulin resistance reduces the action of insulin in peripheral tissues, competing with the hyperglycemia framework with consequent compensatory hyperinsulinemia. Even with its low hypoglycemic action, this hormone is described to act in specific gene transcription and modulation of cell growth and differentiation, which can be overexpressed, such as in cases of breast cancer (26,27).

The increase in free serum insulin also reduces the production of binding proteins, insulin-like growth factor-binding protein 1 (IGFB-1), and insulin-like growth factor-binding protein 2 (IGFB-2), which may increase the availability of insulin-like growth factor (IGF-1) free bioactive, resulting in concomitant changes in the cellular environment that favor the formation of tumors (24,27,28). The bioactive free IGF-1 can bind to its receptor and the insulin receptor, stimulating DNA synthesis and mitosis of preneoplastic and neoplastic mammary cells (28,29). Thus, both the growth factor similar to the insulin receptor and the insulin receptor are frequently overexpressed in neoplastic mammary cells and are also associated with the tumor size and mortality of the disease (27).

Another reason for the association between breast cancer and insulin metabolism involves the hormonal etiology of this disease (10,13). The high serum concentration of insulin and IGF-1 in women with insulin resistance inhibits the synthesis of sex hormone binding globulin (SHBG). This low serum concentration of SHBG can result in increased availability of free bioactive estrogen, which is able to increase the stimulation and density of breast parenchyma (10,24,27).

In a case-control study that included 124 newly diagnosed Mexican women with breast cancer and 197 healthy controls in order to identify the effect of insulin resistance (HOMA-IR > 3.5) in the development of breast cancer, an association between HOMA-IR and the outcome was not observed, regardless of the menopausal status (13). In the current study, there was a significant association between these variables in a univariate analysis, although a HOMA-IR value greater than 2.7 has been considered as a reference. Thus, a reassessment of the reference values of HOMA-IR is suggested, which could add new information about the association between breast cancer and resistance to insulin action.

The hyperglycemia that precedes diagnosis of diabetes was also associated with the diagnosis of breast cancer and can be explained by the "Warburg effect", which is the ability of tumor cells to alter glucose metabolism, giving priority to rapid cell proliferation and uncontrolled tumor growth (27,29).

The association between the lipid profile and breast cancer has been investigated in different population groups (30-33). In the present study, we observed a higher prevalence of low HDL among women newly diagnosed with breast cancer ($p = 0.011$). This lipoprotein fraction may present anti-inflammatory and antioxidant properties and the ability to inhibit cell proliferation (33). In addition, elevated levels of endogenous estrogens are inversely associated with HDL (31). It is noteworthy that the carcinogenesis process can alter the lipid profile, which may start years before the diagnosis of cancer. It is difficult to establish whether chang-

es in HDL concentrations precede or are a consequence of the disease (34). Thus, prospective and larger sample size studies should be conducted to define the relevance of the lipid profile in the tumor biology of breast cancer, as well as the evaluation of serum estrogens.

Among the limitations of the case-control studies, there is the bias of memory and selection. However, the main variables in research were measured. Furthermore, recruitment of patients in both groups involved the same population to ensure similarity between them, especially with regard to age and BMI.

To the best of our knowledge, this is the first study to evaluate the association of the VAI and LAP indicators of breast cancer. In this context, the homogenization of the case and control groups reduced the influence of age and body composition variables in the research. However, prospective studies are needed to establish a better relationship and the impact of these indicators on the development and monitoring of breast cancer.

The results of this study suggest that women with greater deposition of visceral fat have a higher chance of developing breast cancer. Thus, this study highlights the importance of analyzing the body compartments rather than a partial analysis of total body weight.

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