HSJ Health Sciences Journal

HCI HOSPITAL DE CLÍNICAS DE ITAJUBÁ-MG ENSINO E PESQUISA

SYSTEMATIC REVIEW

Metabolic syndrome in women with breast cancer: scope review

Síndrome metabólica em mulheres com câncer de mama: revisão de escopo

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KEYWORDS
Breast Cancer
Metabolic Syndrome
Obesity
Oncology
Metabolic Diseases

ABSTRACT

Objective: To synthesize evidence involving pathophysiological and clinical-epidemiological linking mechanisms in women with breast cancer and metabolic syndrome. **Method:** This is a structured scoping review according to the Joanna Briggs Institute and was conducted in the PubMed, BDENF, LILACS, IBECS, CUMED, WPRIM, BINACIS, and Embase databases. This review is registered in the Open Science Framework. **Result:** Regarding the level of evidence of the included studies, moderate and strong evidence levels were predominant. There were no weak evidence findings in this research. The chronic inflammatory state of breast adipose tissue in patients with obesity can worsen the negative impact on cancer cells, directly affecting survival and recurrence. Unexplained weight gain or loss is associated with shorter survival in women with breast cancer, highlighting the need for specific guidance during treatment. **Conclusion:** Metabolic syndrome is associated with the risk of breast cancer; however, massive weight loss during active disease can be associated with a worse prognosis and should therefore be prevented. Patients should be advised to maintain a stable weight during chemotherapy and to receive guidance on adequate nutrition and physical activity to increase muscle mass.

PALAVRAS-CHAVE
Câncer de Mama
Síndrome Metabólica
Obesidade
Oncologia
Doenças Metabólicas

RESUMO

Objetivo: Sintetizar as principais evidências envolvendo os mecanismos de ligação fisiopatológico e clínico-epidemiológico em mulheres com câncer de mama e a síndrome metabólica. **Método:** Trata-se de uma revisão de escopo estruturada conforme o Instituto Joanna Briggs, realizado nas bases de dados PubMed, BDENF, LILACS, IBECS, CUMED, WPRIM, BINACIS e Embase. Esta revisão encontra-se protocolada no Open Science Framework. **Resultado:** Com relação ao nível de evidência dos estudos inclusos, houve predominância para níveis fortes de evidência. Não houve achados de evidência fraca nesta pesquisa. O estado inflamatório crônico do tecido adiposo mamário em casos de obesidade pode agravar o impacto negativo nas células cancerígenas, afetando diretamente a sobrevida e recorrência. Ganho ou perda de peso inexplicável estão associados a uma menor sobrevida em mulheres com câncer de mama, sublinhando a necessidade de orientações específicas durante o tratamento. **Conclusão:** A síndrome metabólica esta associada ao risco de câncer de mama, entretanto, a perda maciça de peso durante a doença ativa pode ser um fator de pior prognóstico, devendo assim, ser realizada de forma preventiva. Os pacientes devem ser orientados a manter um peso estável durante a quimioterapia e receber orientações sobre alimentação adequada e atividade física em busca de aumento de massa muscular.

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This study was conducted at Universidade Federal do Rio de Janeiro.
Conflicts of interest: No conflicts of interest declared concerning the publication of this article.
Funding information: Nothing to declare.
Submitted 17 Feb 2024, revised 9 June 2024, accepted 9 June 2024, published 27 Aug 2024

How to cite this article: Rezende LDA, Catabriga DS, Barbosa JR, Assis LZA, Bertoldi GC, Fiorin BH. Metabolic syndrome in women with breast cancer: scope review. HSJ. 2024;14:e1535. https://doi.org/10.21876/hsjhci.v14.2024.e1535

INTRODUCTION

Breast cancer is considered an important public health condition given its high incidence among women and worrying morbidity and mortality rates. The 5-year survival rate for metastatic breast cancer is less than 30% even when treated with adjuvant chemotherapy. In 2018, the International Agency for Research on Cancer released data through GLOBOCAN and revealed that in 185 countries there were 2.3 million new cases of breast cancer, with a mortality rate of 6.9%. Therefore, there is a need to develop new strategies to improve quality of life, control complications, and prevent general and oncological mortality[1,2].

In addition to early diagnosis of breast cancer, which is made possible by access to health services and mammographic screening, treatments for the disease significantly increase patient survival when initiated early. In early cases of breast cancer, adjuvant endocrine therapy for 5 years reduces the risk of recurrence in patients with estrogen- and/or progesterone receptor-positive breast cancer, as measured by immunohistochemistry[2,3].

Patients diagnosed with breast cancer have a greater association with metabolic syndrome, and this relationship is particularly evident in postmenopausal women. Metabolic syndrome is defined by a set of metabolic risk factors, including abdominal obesity, dyslipidemia, hypertension, and hyperglycemia, that significantly increase the outcomes of cardiovascular mortality, such as acute myocardial infarction and stroke. Thus, women who undergo treatment for breast cancer have a higher risk of developing metabolic syndrome and poor overall survival[3,4].

Given the clinical and epidemiological importance of obesity and its link to breast cancer, this study aimed to synthesize the main evidence to elucidate the mechanisms and to understand the relationship between metabolic syndrome and breast cancer.

METHODS

This scoping review had its research protocol registered in the Open Science Framework on 11 May 2023 under DOI: 10.17605/OSF.IO/YPNG9. The research ethics committee approval was not needed. This review was developed based on the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) and the review method proposed by the Joanna Briggs Institute (JBI) for scoping reviews[5].

To guide the formulation of the guiding question, the PECO (Population/Exposure/Comparison/Outcomes) mnemonic strategy was adopted, considering P = (People with breast cancer), E = (Metabolic syndrome associated with breast cancer), C = (Breast cancer patients without metabolic syndrome), and O = (Metabolic syndrome worsens prognosis). Thus, the following guiding question was summarized: "What is the evidence about the development of metabolic syndrome in breast cancer patients?"[6-8].

Eligibility of studies

Primary quantitative or qualitative studies were included. Technical and government documents were considered, as were theses and dissertations. Preprints were excluded, and there was a time limit of 10 years of publication, where the main publications on the subject can be found. To cover the review, there were no language restrictions.

Collecting and extracting data from the studies

The search was conducted in May 2023 in the Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed, Cochrane Library, Nursing Database (BDENF), Latin American and Caribbean Literature in Health Sciences (LILACS), Índice Bibliográfico Español en Ciencias de la Salud (IBECS), *Centro Nacional de Información de Ciencias Médicas de Cuba* (CUMED), *Index Medicus del Pacífico Occidental (WPRIM) and Bibliografía Nacional en Ciencias de la Salud Argenti*na (BINACIS) and Embase.

To search the databases, the following Medical Subject Headings (and its Portuguese counterparts in the *Descritores em Ciências da Saúde*) were chosen: "Breast Cancer"/"Cancer de Mama", "Metabolic Syndrome"/"Sindrome Metabólica", "Cardiometabolic Syndrome"/"Síndrome Cardiometabólica" and "Obesity"/"Obesidade". For the search, the descriptors were separated by Boolean operators, and the search was summarized as follows: (Breast Cancer) AND (Metabolic Syndrome OR Cardiometabolic Syndrome OR Obesity) / (Câncer de Mama) AND (Síndrome Metabólica OR Síndrome Cardiometabólica OR Obesidade).

To facilitate the article selection process, data were collected and extracted using Rayyan™ software, thereby favoring independent and double-blind selection. The selection of studies was carried out by the researchers LDAR and BHF who are experienced in this research field. Duplicate articles were selected and excluded using Mendeley Reference Management Software.

The articles were first screened using the title and abstract, including those that answered the guiding question and corroborated the inclusion criteria. A second screening was then carried out by evaluating the full text. In the event of disagreement between the authors, a third author was consulted.

Data extraction, analysis, and synthesis

Data were extracted using a previously published form[8]. The extracted data included the name of the authors, impact factor (JCR 2020), year of publication, country, objectives, antineoplastic used, methodological design, sample size (if applicable), collection period, main results, study limitations, conclusion and implications for clinical practice, and level of methodological evidence.

The classification of evidence was based on study hierarchy and study design. This method classifies studies into 7 levels, from I to VII, as described in Table 1. In this review, we considered levels I–III as strong, IV–VI as moderate, and VII as weak. The data were summarized descriptively and tabulated in the Results. The table contains (a) author/year; (b) country of the main author; (c) objective; (d) clinical applicability; (e) methodological design (f) level of evidence, and (g) JCR. Tables 2 and 3 present the extracted compiled data.

The quality assessment of the productions was carried out following Law et al.[25], as well as removing

Table 1 – Hierarchical level and study design.

Level of evidence Study design	Level of evidence Study design
I	Systematic reviews or meta-analyses of randomized clinical trials
II	Well-designed randomized controlled trial
III	Well-designed non-randomized controlled clinical trial
IV	Well-designed cohort, case-control, cross-sectional study
V	A systematic review of qualitative studies and descriptive studies
VI	A single descriptive or qualitative study
VII	Expert opinion and/or expert report.

Table 2 – Characteristics of the selected studies.

Main author and year of publication	Country	Objectives	Clinical applicability
Brown (2021)[9]	United States of America	Explain the metabolic pathways of obesity-related breast cancer	It provides a theoretical basis for the main pathways for the development of obesity in people with breast cancer and encourages the development of new research on the subject.
Iwase et al. (2021)[10]	United States of America	Clarify the association between body composition and the risk of breast cancer treatment	Helps to better understand the biology of body composition phenotypes, which is fundamental for determining the best intervention program for patients with breast cancer
Fallone et al. (2018)[11]	France	Elucidate and summarize data on the metabolic syndrome associated with breast cancer and the influence of the chronic sub-inflammatory state on breast cancer.	In obesity, the chronic sub-inflammatory state of the surrounding breast adipose tissue could amplify the negative effect of crosstalk between cancer cells
Pang et al. (2022)[12]	China	To investigate the associations between general and central adiposity before and after diagnosis of breast cancer, weight change, and mortality.	Higher adiposity was associated with all-cause mortality, as well as distant recurrence.
McTiernan (2018)[13]	United States of America	To expose the literature on the associations between weight, physical activity, and prognostic variables in breast cancer in women	Weight gain and unexplained weight loss were associated with poorer survival in women with breast cancer. Most individual patients should be advised to avoid weight gain during the cancer treatment process.
Ryu et al. (2021)[14]	South Korea	To compare changes in the metabolic profile and neutrophil-lymphocyte ratio between patients undergoing neoadjuvant chemotherapy and neoadjuvant endocrine therapy 3 years after breast cancer treatment.	The neutrophil-lymphocyte ratio worsened metabolic profile parameters such as body mass index, triglycerides and fasting glucose, which are recovered over 3 years. There were no changes in metabolic rate when using neoadjuvant endocrine therapy.
Martel et al. (2021)[15]	Canada	To determine the impact of body mass index at the start of the study and weight change after 2 years on the outcomes of patients with HER2-positive early breast cancer.	In patients with HER2-positive early breast cancer, obesity was a poor prognostic factor. Weight loss during treatment and follow-up impairs clinical outcomes.
Chan et al. (2023)[16]	United Kingdom	To assess body fat, dietary changes, and weight changes in patients with breast cancer.	Higher post-diagnosis body fat increased the risk of all-cause and breast cancer mortality.
Becerril-Alarcón et al. (2019)[17]	Mexico	To determine whether inulin supplementation prevents blood pressure elevation in women with breast cancer undergoing neoadjuvant therapy with cyclophosphamide and doxorubicin.	Inulin supplementation reduced SBP and prevents increases in DBP in women with breast cancer.
Ginzac et al. (2018)[18]	France	To evaluate the evolution of body composition and weight in postmenopausal patients with breast cancer who received endocrine therapy after chemotherapy with taxanes.	Overweight and obese patients and those who lost weight during chemotherapy were more likely to gain weight and fat mass during endocrine therapy.

Table 2– Continued...

Main author and year of publication	Country	Objectives	Clinical applicability
Mutschler et al. (2018)[19]	Germany	To evaluate the influence of weight changes during adjuvant chemotherapy in patients with breast cancer.	Weight gain of more than 5% during adjuvant chemotherapy in patients with high-risk early breast cancer was associated with a worse outcome.
Silva and Figueiredo (2021)[20]	Brazil	To verify the prevalence of MetS and cardiovascular disease in breast cancer survivors.	There was a higher prevalence of metabolic syndrome in breast cancer survivors due to excess weight.
Zhao et al. (2020)[21]	China	To assess the risk of patients with MetS developing breast cancer	MetS was highly related to breast cancer. In postmenopausal patients with 2 or more components of MetS or a combination of obesity, hypertension, and diabetes, routine breast cancer screening can help detect breast cancer at an early stage.
Yee et al. (2020)[22]	United States of America	Review the literature on the controversial relationship between breast cancer and obesity, and the impact of insulin on the oncological and subcellular components of breast cancer.	Insulin plays an important role in driving the biological signaling pathways of breast cancer. Although it is not standard to test for insulin resistance during breast cancer screening and treatment, attention should be paid to this point.
Kaul et al. (2021)[23]	United States of America	Discuss the pathological mechanisms identified in the tumor microenvironment as well as in the obese microenvironment that contribute to the development and progression of triple-negative breast cancer.	Obesity appears to influence several pathological pathways, ranging from insulin resistance and survival pathways to fatty acid oxidation and immune system activation, as well as increasing the risk of poor prognosis in breast cancer.
Lohmann et al. (2021)[24]	Canada	To evaluate the association of obesity or overweight at diagnosis of non-metastatic breast cancer with disease-free survival and overall survival.	Obesity was associated with worse disease-free survival and survival in all subtypes of breast cancer.

Table 3– Methodological characteristics of the selected studies.

Study	Methodological design	Evidence level	Impact factor (2023)
Brown[9]	Literature review without meta-analysis and without specifying the number of studies	V	47.5
Iwase et al.[10]	Literature review without meta-analysis and without specifying the number of studies	V	3.8
Fallone et al.[11]	Literature review without meta-analysis and without specifying the number of studies	V	0.71
Pang et al.[12]	Literature review with meta-analysis and 173 studies included	I	3.8
McTiernan[13]	Literature review without meta-analysis and without specifying the number of studies	V	6.391
Ryu et al.[14]	A well-designed randomized clinical trial with 123 participants.	II	4.6
Martel et al.[15]	A well-designed randomized clinical trial with 8,381 participants.	II	12.69
Chan et al.[16]	Literature review with meta-analysis and 225 studies included.	I	7.316
Becerril-Alarcón et al.[17]	A well-designed randomized clinical trial with 38 participants.	II	3.1
Ginzac et al.[18]	A well-designed non-randomized clinical trial with 33 participants	III	3.3
Mutschler et al.[19]	A well-designed randomized clinical trial with 1,493 participants.	II	3.3
Silva and Figueiredo[20]	A prospective cohort with 120 participants.	IV	0.131
Zhao et al.[21]	Literature review with meta-analysis and 25 studies included.	I	4.807
Yee et al.[22]	Literature review without meta-analysis and without specifying the number of studies.	V	6.055
Kaul et al.[23]	Literature review without meta-analysis and without specifying the number of studies.	V	9.7
Lohmann et al.[24]	Literature review with meta-analysis and 27 studies included.	I	10.3

HSJ. 2024;14:e1535 | https://doi.org/10.21876/hsjhci.v14.2024.e1535

the assessment score in cases of non-applicability of the criteria, as shown in Table 4.

RESULTS

Search results

The search of the nine databases identified 755 articles, of which 131 duplicates were excluded. The remaining 624 articles were analyzed according to their titles, and 600 articles were excluded because they were not compatible with the guiding question. Therefore, 24 studies were analyzed according to the abstract and full reading, excluding 8 that did not address the topic. Thus, 16 articles were included for the scoping review. The PRISMA-ScR flowchart is shown in Figure 1.

Characteristics of the studies

The most predominant year of publication was 2021 (n=7), followed by 2018 (3), 2019 (2), 2020 (2), 2021 (n=1), and 2023 (1).

Among the countries in which the study was concentrated, we have the United States of America with 5 articles, China, Canada, and France with 2 articles each, and Brazil, Germany, South Korea, Mexico, and the United Kingdom with 1 article each.

When analyzing the study population, all selected studies included women over 19 years and did not exclude postmenopausal or premenopausal women.

Most included studies were literature reviews without meta-analysis (6), followed by systematic reviews with meta-analysis (4) and randomized clinical trials (4). Other types of methodology were non-randomized clinical trials and cohort studies (1 each).

When evaluating the evidence level of the included studies, the predominance of studies converged toward strong levels: NE I (25%), NE II (25%), and NE III (6.25%). The moderate levels of evidence were NE V (37.5%) and NE IV (3.25%). There were no findings of weak evidence during this study.

In terms of methodological quality, based on the generic quantitative assessment tool, 6 studies were of moderate quality and 10 were of good quality. Table 4 presents the methodological assessment based on the Law et al. generic tool[25].

DISCUSSION

Based on the results, this study provides a solid foundation for the interconnections between obesity and breast cancer. These findings highlight the importance of understanding the relationship between obesity and breast cancer development. The chronic inflammatory state of breast adipose tissue in patients with obesity can intensify the negative impact on cancer cells, directly affecting survival and recurrence. Unexplained weight gain or loss is associated with poor survival in women with breast cancer, highlighting the need for specific treatment guidelines. The neutrophil-lymphocyte relationship, the influence of obesity on various pathological pathways, and its impact on clinical outcomes highlight the critical relevance of weight management for improving outcomes and survival in patients with breast cancer.

Table 4 – Quantitative assessment of the studies included in the review.

Study	Criteria*												Score	%
	1	2	3	4	5	6	7	8	9	10	11	12		
Brown[9]	Y	Y	N	N	N	NA	NA	N	Y	Y	NI	Y	5/10	50%
Iwase et al.[10]	Y	Y	N	N	N	NA	NA	N	Y	Y	NI	Y	5/10	50%
Fallone et al.[11]	Y	Y	N	N	N	NA	NA	N	Y	Y	NI	Y	5/10	50%
Pang et al.[12]	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	11/11	100%
McTiernan[13]	Y	Y	N	N	Y	NA	NA	Y	Y	Y	NI	Y	7/10	70%
Ryu et al.[14]	Y	Y	Y	Y	Y	Y	NI	Y	Y	Y	NI	Y	10/12	83.3%
Martel et al.[15]	Y	Y	Y	Y	Y	Y	NI	Y	Y	Y	NI	Y	10/12	83.3%
Chan et al.[16]	Y	Y	Y	Y	Y	NA	NA	Y	Y	Y	NI	Y	9/10	90%
Becerril-Alarcón et al.[17]	Y	Y	Y	Y	Y	Y	NI	Y	Y	Y	Y	Y	11/12	91.6%
Ginzac et al.[18]	Y	Y	N	Y	N	N	Y	Y	N	Y	NI	N	6/12	50%
Mutschler et al.[19]	Y	Y	Y	Y	Y	Y	NI	Y	Y	Y	Y	Y	11/12	91.6%
Silva and Figueiredo[20]	Y	Y	Y	Y	N	Y	NI	Y	Y	Y	NI	Y	09/12	75%
Zhao et al.[21]	Y	Y	Y	Y	Y	NA	NA	Y	Y	Y	Y	Y	10/10	100%
Yee et al.[22]	Y	Y	N	N	N	NA	NA	Y	Y	Y	N	Y	6/10	60%
Kaul et al.[23]	Y	Y	N	N	N	NA	NA	N	Y	Y	NI	Y	5/10	50%
Lohmann et al.[24]	Y	Y	Y	Y	Y	NA	NA	Y	Y	Y	Y	N	09/10	90%

N: No. NA: Not Applicable. NI: Not Informed. Y: Yes. Study classification: ≥70%: Good quality; ≥50% and <70%: Moderate quality; <50%: Poor quality. *Criteria: 1 = Study objective; 2 = Relevant background; 3 = Sample description; 4 = Sample size justification; 5 = Reliability and validity of outcome measures; 6 = Intervention description; 7 = Contamination and co-intervention; 8 = Statistical significance; 9 = Appropriate analyses; 10 = Clinical-epidemiological significance; 11 = Dropouts reported; 12 = Appropriate conclusions.

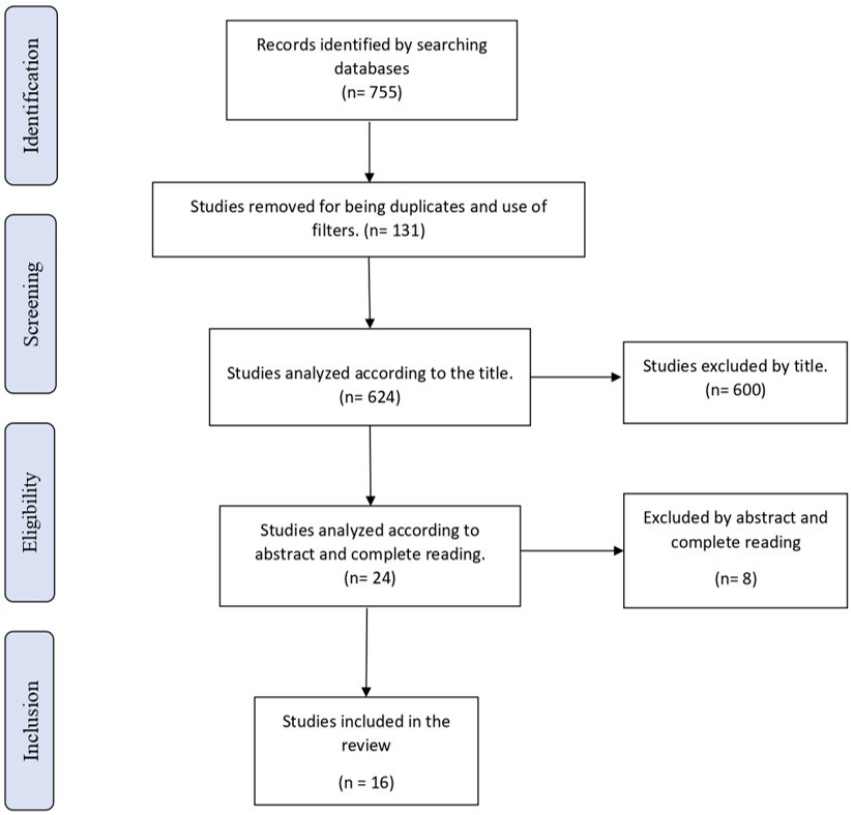

Figure 1 – Selection steps according to PRISMA - Extension for Scoping Reviews (PRISMA-ScR).

Breast cancer microenvironment and adiposity: signaling pathways

Increased insulin levels can stimulate proliferation pathways and inhibit apoptosis, leading to the growth and progression of pre-existing tumors[23]. However, it is necessary to understand the tumor microenvironment that drives tumor progression, so the effects of growth factors derived from adipose tissue will be discussed in this section.

Much attention has been paid to characterizing the metabolic changes that occur in cancer, including understanding how and why some cells change their mode of energy production, moving away from mitochondrial respiration and toward glycolysis, which is independent of oxygen and is called the Warburg effect[9,26]. The hypoxic microenvironment in which a malignant or premalignant lesion is located creates a selective pressure that drives its metabolism toward glycolysis[26].

Although glycolysis is less efficient than respiration in producing ATP, increased glucose uptake, often in excess, allows cancer cells to generate not only sufficient levels of ATP but also metabolic intermediates that can be used for the biosynthesis of nucleotides, amino acids, and fatty acids necessary for cell division. Any excess glycolytic by-products are secreted into the extracellular space as lactate, which can also serve as an energy source by neighboring proliferating cells[9]. Thus, the Warburg effect also corroborates the proliferation of breast tumors and their metastatic evolution[26,27].

Obesity is associated with various systemic and local changes that contribute to cancer-support pathways. Excess energy availability associated with the onset of obesity can result in hyperglycemia and hyperinsulinemia, and an increase in adipose tissue[9,11,22,28].

The expansion of adipose tissue requires angiogenesis to increase the supply of nutrients and oxygen to proliferating adipocyte precursors. Angiogenesis is a normal attribute of tissue development and occurs because of the release of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF). However, adipocytes have a finite capacity to store lipids, and in cases of large lipid droplets, they become hypoxic[9].

Intracellular hypoxia stabilizes hypoxia-inducible factor-1 alpha (HIF-1α), a key regulator of VEGF expression in most tissues. However, the expansion of adipose tissue in obesity and the stabilization of HIF-1α in adipocytes are associated with fibrotic and inflammatory rather than pro-angiogenic responses, suggesting that the control of VEGF in adipose tissue is independent of HIF-1α[29].

Increased expression of HIF-1α in adipocytes positively regulates the production of pro-inflammatory factors tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). Consequently, MCP-1 recruits macrophages to the tissue

HSJ. 2024;14:e1535 | https://doi.org/10.21876/hsjhci.v14.2024.e1535

microenvironment, and these macrophages tend to form a crown-like structure by phagocytizing dead adipocytes[10,29].

Consequently, HIF-α activates the profibrotic pathway, remodeling the extracellular matrix (ECM) into a chronic inflammatory state, which can lead to the development, progression, resistance to treatment, and metastasis of breast cancer. Dysfunctional adipose tissue accumulates pro-inflammatory cytokines, including IL-6 and TNF-α, which accelerate sarcopenia. IL-6 directly impairs the biological activity of IGF-1 and decreases its anabolic effect on skeletal muscle. Inhibition of protein synthesis is also induced by TNF-α[10,11,29]. The entire pathway of breast cancer drivers in obesity is illustrated in Figure 2.

When exploring cell metabolism, we observed that the transcription factor HIF-1α plays a crucial role in optimizing the efficiency of the electron transport chain by promoting modifications in the subunits of cytochrome c-oxidase. In addition, HIF1-α has a direct influence on glycolysis and the tricarboxylic acid cycle, inducing the expression of enzymes such as lactate dehydrogenase A and PDK1. Because of these alterations, glucose tends to be predominantly converted to lactate, whereas the flow through the tricarboxylic acid cycle is reduced[31].

In the early stages of cancer development, vascular deficiency associated with rapid tumor cell growth results in low oxygen and nutrient scarcity. In this scenario, HIF-1α triggers glucose uptake and increased glycolytic flux, promoting elevated expression of transporters such as GLUT1 and GLUT3 and enzymes such as HK1, HK2, enolase 1, phosphoglycerate kinase 1, PKM2, and LDHA. Essentially, HIF-1α reconfigures cellular metabolism to adapt to the specific demands of growing tumor cells[9,31].

Induced hypoxia and apoptosis-induced cell death lead to the release of chemokines such as monocyte chemoattractant protein 1 (MCP1), which induces the recruitment of immune cells that secrete inflammatory components. Increased body mass is associated with increased production of adipokine by fat cells. The best characterized of these adipokine is leptin, a peptide hormone that induces feelings of satiety in healthy individuals. In individuals with obesity, leptin cannot perform the function owing to the development of leptin resistance in the central nervous system[32,33].

Adipose tissue, particularly in individuals with obesity, secretes various factors such as growth hormones and cytokines such as leptin, CCL-5, and IL-6, which contribute to increased energy intake and cell replication[32]. Increased insulin resistance associated with hyperinsulinemia in obese individuals results in high blood lipid and glucose in the bloodstream. It also promotes the stimulation of survival pathways through AKT/PI3K signaling. The cytokines induced by obesity influence immune cells, contributing to the targeting and polarization of immunosuppressive cells in the tumor stroma[11,23].

The overlapping tumor microenvironment associated with obesity leads to enhanced signaling of tissue growth pathways such as PI3K, mTOR, AKT, MAPK, NF-B, and their downstream pathways[23,34]. This in turn contributes to the migration and survival of cancer cells, immunosuppression, and metabolic reprograming, which can generate a more aggressive cancer phenotype and resistance to cytotoxic drugs[23].

Body composition and its relationship with breast cancer

Given the etiological implications of metabolic syndrome in the development of breast neoplasms, it is

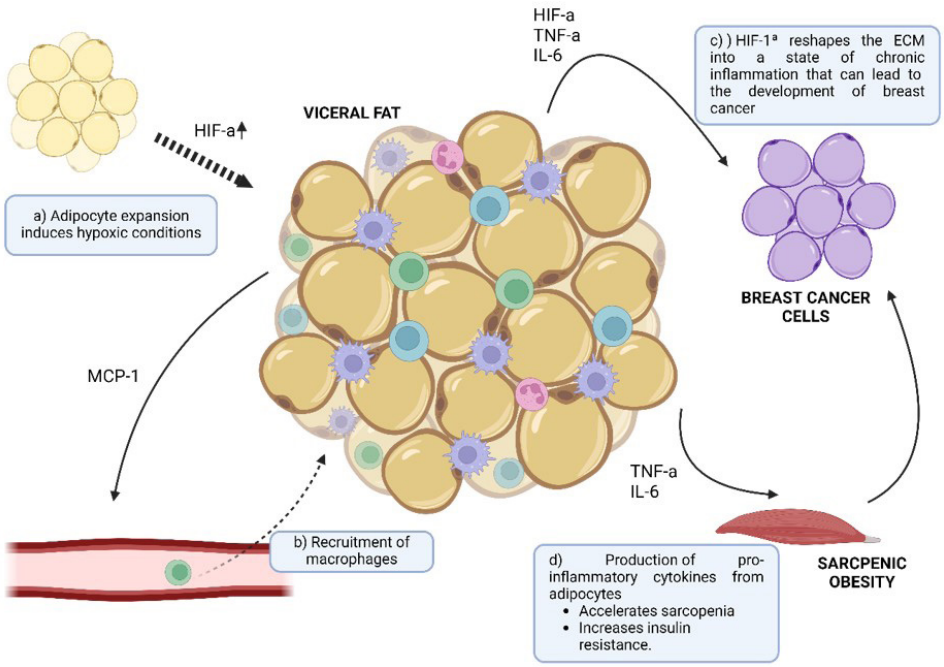

Figure 2 – Microenvironment and drivers of breast cancer in obesity.
Source: Author (2024). Created with BioRender[30].

possible to understand that MetS is related to an increased incidence of breast neoplasms in postmenopausal women compared with patients without MetS. The number of MetS components in patient increases with the risk of breast cancer. The independent factors most associated with breast cancer are obesity, diabetes, and hypertension. However, it is unclear whether only one characteristic of the syndrome increases risk. In women with hyperinsulinemia and hyperglycemia, the risk of developing breast cancer is doubled[21,22].

Obesity is associated with worse overall and disease-free survival in all types of breast cancer[16,24]. This may be due to the high risk of various complications, such as lymphedema, healing disorders, and even the risk of developing recurrences or other cancers associated with metabolic syndrome, such as endometrial, colon, and kidney cancers, among others[13]. In patients with hormone receptor-negative Her2 and triple-negative tumors, obesity is associated with lower breast cancer-specific survival[24].

Based on the mechanisms discussed, it can be inferred that weight gain is associated with worse prognosis and survival in patients with BC, which has also been described in observational studies. In patients who receive adjuvant chemotherapy and then endocrine therapy, the latter stage is the main cause of fat mass gain. In other studies with HER2-positive patients, however, weight gain did not result in significant changes in overall survival[13].

However, weight loss has also been associated with a worse prognosis, leading to an increase in overall mortality regardless of BMI at diagnosis[13], especially if this loss is greater than 10% of the initial weight[15,19]. One explanation for this finding could be the increase in fat mass following this weight loss, especially in patients who were overweight or obese at the time of diagnosis. Energy restriction during chemotherapy can also increase visceral fat deposits via fat overshoot[18].

Obesity and different body composition phenotypes can have different impacts on breast cancer progression. In organisms with visceral obesity, rapid expansion and apoptosis of adipocytes occur, which summons the immune system and generates a microenvironment rich in activated macrophages, leading to high pro-inflammatory activity. In addition, there is marked profibrotic activity, which can result in the development and progression of breast cancer, resistance to treatment, and metastasis, contributing to a significant increase in overall mortality, as observed in the studies analyzed[11,12].

In other obesity phenotypes, such as sarcopenic obesity, the increase in pro-inflammatory factors can increase the risk of neoplasms, especially in older people, and can contribute to maintaining or worsening MetS because lipid replacement can cause greater insulin resistance[10].

MetS not only affects patient survival during disease but also exposes patients undergoing treatment and cancer survivors to a greater risk of developing MetS than older women without a diagnosis. Breast cancer survivors exhibited increased BMI, waist circumference, and dyslipidemia. This trend can be attributed to prolonged inactivity caused by treatment, such as fatigue and pain[20].

Other factors also included in MetS, such as hypertension, show a significant increase in patients undergoing neoadjuvant chemotherapy or neoadjuvant hormonal therapy[14]. Clinical trials have studied the effectiveness of inulin therapies and have shown a significant reduction in systolic blood pressure, as well as attenuation of increases in diastolic and mean arterial pressure. Fiber supplementation has also been shown to reduce blood pressure. The use of these substances in treatment could be beneficial in promoting the long-term quality of life of patients with breast cancer, especially in those whose therapeutic plans include chemotherapy or neoadjuvant endocrine therapy[17].

Additional studies have indicated that the neutrophil-lymphocyte ratio is not only a marker of poor prognosis but also a significant indicator of progression to insulin resistance. This finding suggests the possibility of using this indicator as a valuable tool for identifying patients who could benefit from specific therapeutic approaches, particularly those exposed to neoadjuvant chemotherapy. Understanding the interconnection between neutrophil-to-lymphocyte ratio and insulin resistance may offer crucial insights for developing personalized treatment strategies aimed not only at fighting cancer but also at effectively managing the metabolic complications associated with treatment[17,21,35].

CONCLUSION

Several risk factors contribute to the development of cancer, and it is therefore necessary to emphasize its effective prevention. Our study showed that metabolic syndrome is highly associated with the risk of breast cancer; however, massive weight loss during the active neoplastic process may be a prognostic factor that should be prevented.

Thus, patients should be advised to maintain a stable weight during chemotherapy and should receive guidance on proper nutrition and exercise to increase muscle mass. Patients who experience weight changes during chemotherapy should receive specific attention and adequate support. As a preventative measure, people with a higher risk of breast cancer should have strict control of cardiometabolic factors and should adopt a healthy lifestyle to reduce the risk of breast cancer.

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