Body Mass Index and Metabolic Phenotypes in Breast Cancer Risk: A Meta-Analysis and Systematic Review

Víctor Juan Vera-Ponce[1,2,*], Joan A. Loayza-Castro[1,2], Luisa Erika Milagros Vásquez-Romero[1,2] and Fiorella Elvira Zuzunaga-Montoya[1,2]

[1]*Instituto de Investigación de Enfermedades Tropicales, Universidad Nacional Toribio Rodríguez de Mendoza de Amazonas (UNTRM), Amazonas, Perú*

[2]*Facultad de Medicina (FAMED), Universidad Nacional Toribio Rodríguez de Mendoza de Amazonas (UNTRM), Amazonas, Perú*

Abstract: *Introduction*: Numerous studies have established that obesity, often assessed through body mass index (BMI), is one of the most significant risk factors for the development of breast cancer (BC). However, not all individuals with obesity have the same risk of developing BC and vice versa.

Objective: To determine the association between metabolic states and the risk of BC.

Materials: AS systematic review (SR) with a meta-analysis of cohort studies was conducted. The search was performed in four databases: PubMed/Medline, SCOPUS, Web of Science, and EMBASE. Metabolic states were classified as Metabolically Healthy Normal Weight (MHNW), Metabolically Unhealthy Normal Weight (MUNW), Metabolically Healthy Obesity (MHO), and Metabolically Unhealthy Obesity (MUO). Association measures were presented as hazard ratios (HR) with their 95% confidence intervals (CI95%).

Results: A total of four studies were evaluated. The meta-analysis found a statistically significant association between the development of BC and the MHO state (HR: 1.14; CI95% 1.02, 1.28) and MUO state (HR: 1.37; CI95% 1.16, 1.62) compared to individuals with MHNW. No association was found with the MUNW state.

Conclusions: The findings suggest that obesity, as determined by BMI, is significantly associated with an increased risk of BC, regardless of metabolic state. Additionally, metabolically unhealthy states, especially in obese individuals, appear to increase the risk of BC. Proposed mechanisms include systemic inflammation, metabolic dysfunction, and altered hormone production. These results have important public health implications, emphasizing the need for prevention strategies focused on obesity management and awareness of its associated BC risks.

Keywords: Obesity, metabolism, overweight, Breast Neoplasms (Source: MeSH NLM).

INTRODUCTION

Breast cancer (BC) is the most common type of cancer among women and one of the leading causes of cancer-related deaths in women worldwide [1]. It is defined as a type of cancer that starts in the breast cells, typically in the ducts that carry milk to the nipples or in the glands that produce milk [2]. According to the World Health Organization, over 2 million new cases of BC were diagnosed in 2018, and it caused 627,000 deaths [3]. The number of cases is projected to increase by more than 50% by 2030 due to population aging and growth [4].

In Latin America and the Caribbean, BC is also the most common cancer among women [5]. It is estimated that over 464,000 new cases of BC were diagnosed in the region in 2018, and the incidence is expected to increase by more than 70% by 2040 due to demographic changes [4].

Numerous studies have established that obesity, often assessed through body mass index (BMI), is one of the most significant risk factors for the development of BC [6-8]. However, not all obese individuals have the same risk of developing BC, and conversely, not all individuals with BC have a history of obesity. Therefore, BC risk cannot be solely attributed to weight or BMI [9-12]. This observation has led researchers to distinguish different phenotypes or metabolic states that explain variations in metabolic risk among individuals with different body sizes [13].

Thus, BC risk cannot be anticipated solely based on weight or BMI. Metabolic phenotypes could provide a more accurate tool for identifying individuals at higher risk of developing BC, enabling more effective and targeted preventive interventions. This systematic review and meta-analysis aims to provide a comprehensive perspective on the relationship between these metabolic phenotypes and BC risk.

METHODS

A systematic review (SR) with a meta-analysis of cohort studies was conducted. The PRISMA statement

Address correspondence to this author at the Universidad Tecnológica del Perú, Lima, Peru: E-mail: vicvepo@gmail.com

(Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was used to inform the structure of this work [14].

Search Strategy

This study used search strategies in four databases: PubMed/Medline, SCOPUS, Web of Science, and EMBASE. The key search terms "metabolic phenotype" and "breast cancer" were used. The specific search strategies used for each database are available in Supplementary Material 1.

Selection Criteria

Studies were considered eligible for this SR if they met the following criteria: 1) cohort design; 2) analyzed the relationship between metabolically healthy (MH) and metabolically unhealthy (MU) phenotypes and BC; 3) stratified by body mass index (BMI); 4) included individuals aged 18 years and older; 5) reported hazard ratio (HR), relative risk (RR), or odds ratio (OR); 6) diagnosed BC by biopsy. Research papers were excluded if they were: 1) letters to the editor, conference abstracts, protocols, or review studies; 2) articles that did not provide inferential statistics and measures of association; 3) articles without an abstract and full text in Spanish or English.

Metabolic states were classified into six groups: metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy obesity (MHO), and metabolically unhealthy obesity (MUO). If the terminology used in the studies differed, they were unified according to these nomenclatures. Additionally, it was not an absolute requirement that all studies used the same thresholds to determine normal weight or obesity, nor was the same criterion for "metabolically unhealthy" applied rigidly. This flexibility allowed the inclusion of a broader spectrum of studies in our analysis.

Study Selection

The articles obtained from the different consulted databases were stored using Rayyan software (https://rayyan.qcri.org). Three researchers independently reviewed the titles and abstracts of the documents. If all agreed that a document was suitable for inclusion, it was included. Otherwise, it was discarded. If a discrepancy arose, the co-authors met to reach a consensus regarding that document. Only one was chosen if different studies using the same database were found.

Next, the full text of all preselected articles was reviewed. The decision on whether to include the study or not was recorded in an-Excel sheet. This process was carried out in the same manner as the previous process.

Data Extraction and Qualitative Analysis

The articles that remained proceeded to data extraction using a Microsoft Excel 2022 form. The following information was extracted from each selected article: first author, year, country, design, follow-up time, sample, population (selection criteria), sex (% female), age at cohort start, definition of normal weight, overweight, and obesity, definition of metabolically unhealthy, BC incidence, BC evaluation, adjustment variables.

Risk of Bias Assessment

Three reviewers independently conducted a risk of bias assessment for each included study, discussing their conclusions until consensus was reached. The New Castle Ottawa (NCO) risk of bias assessment tool for cohort studies was used for this evaluation [15]. Generally, the NCO tool assesses a study's risk of bias based on three main criteria: 1) study selection: checking sample representativeness, choice of non-exposed, and exposure validation; 2) comparability: assessing whether confounding factors were adequately controlled during study design or analysis; 3) outcomes: examining how outcomes were assessed, the follow-up period of participants, and whether loss of participants during this follow-up was considered. Each criterion is evaluated based on several sub-criteria, and studies receive stars for each sub-criterion met. Studies accumulating ≥ 7 stars are considered low risk of bias.

Quantitative Analysis

Evaluations were conducted using RevMan 5.3. The variables of interest were handled binarily. BC was the outcome variable, and the metabolic state was the dependent variable. Measures of association were expressed as hazard ratio (HR) with 95% confidence intervals (CI 95%).

To assess heterogeneity among the selected cohort studies, Cochran's Q test and the I2 statistic were used [16]. Heterogeneity was considered significant if I2 > 50% [17]. Due to heterogeneity, results were reported using DerSimonian and Laird's random-effects models.

RESULTS

Eligible Studies

Using the previously mentioned search strategies, 3,468 publications were initially identified. After filtering for titles, abstracts, and duplicates, 2,574 publications were removed. During full-text selection, 49 studies were excluded. Thus, 4 studies were included [9–12] (Figure **1**).

Study Characteristics

Table **1** shows the main characteristics of the studies. A total of 3,159,879 individuals from the United States [9, 10], South Korea [11], and Europe [12] were included. Four cohort studies were included, with follow-up periods ranging from 6.4 to 40 years.

The definition of normal weight, overweight, and obesity was standardized using the classic criterion of <25 kg/m², 25–29.9 kg/m², and ≥30 kg/m² in the studies by Sun *et al*. [12] and Kabat *et al*. [10]; whereas Park B *et al*. [11] and Park Y *et al*. [9] classified it as normal weight (<25 kg/m²) versus overweight/obesity (≥25 kg/m²).

For the definition of metabolically unhealthy, two studies used the criteria from the third report of the National Cholesterol Education Program Adult Treatment Panel III (ATP III), one used the condition of 1 or more cardiometabolic abnormalities, and Sun M *et al*. [12] used the upper tertile of the metabolic score. The rest of the summary is shown in Table **1**.

Risk of Bias Assessment

The included studies showed few variations in overall quality, as they were similar in study design, methodology, and structure. The study by Sun M *et al*. [12] controlled only for age and smoking activity. The bias analysis is shown in Table **2**.

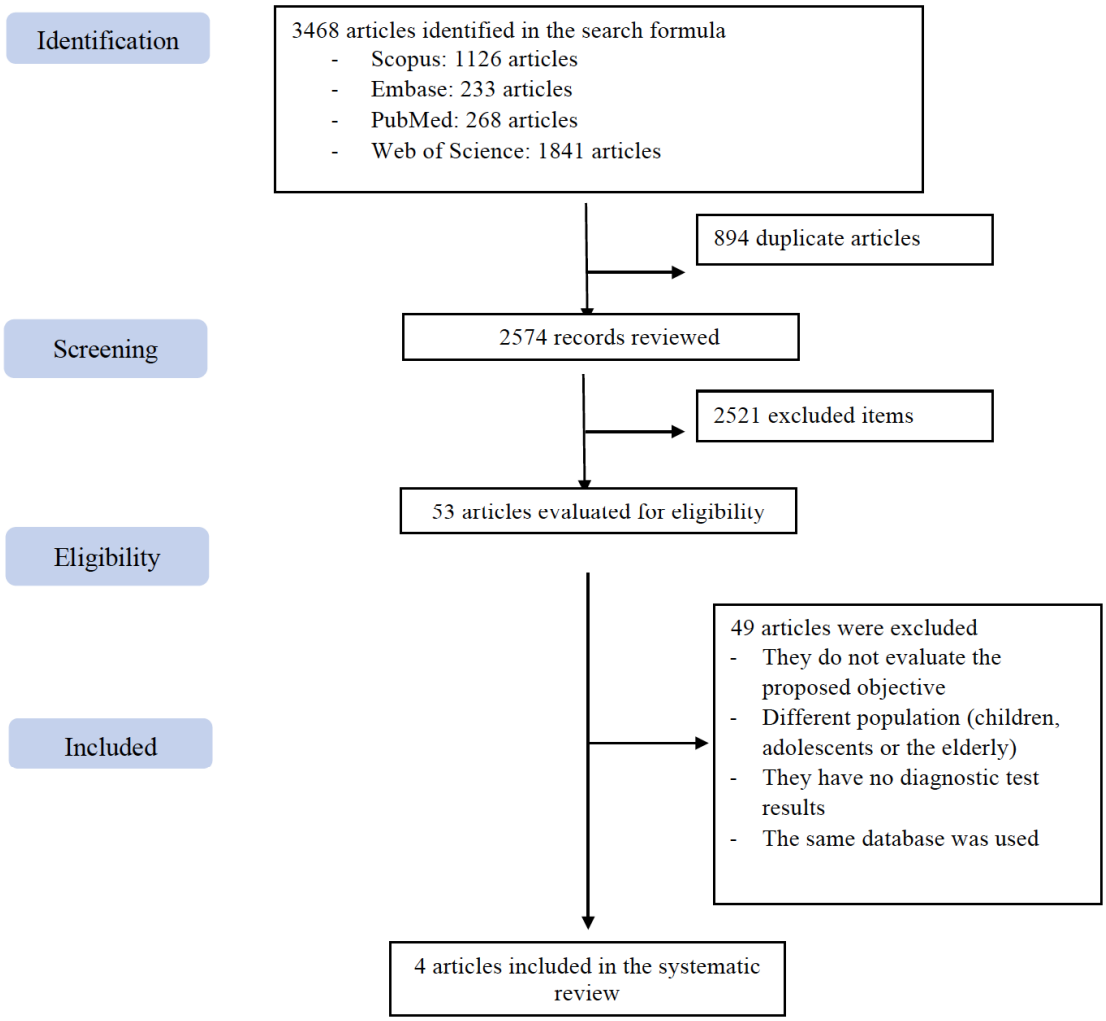

Figure 1: Flowchart.

Table 1: Description of the Studies Included in the Systematic Review

First Author, year	Country	Follow up time (mean or median)	Sample	Population (selection criteria)	Age at cohort entry	Definition of normal weight, overweight and obesity	Definition of metabolic unhealthy	Incidence of breast cancer (%)	Breast cancer ascertainment	Association measure	Adjustment variables
Park, 2017	USA	6.4 years	43,599	People who have aged 25 to 64 years were incluyed People who had incomplete information, have unclear menopausal status, pregnant, breast feeding, who were underweight or who had a history of any cancer except non-melanoma skin cancer were excluyed	MHNW: 53 (± 8.8) MUNW: 60.2 (± 8.2) MHO: 53.4 (± 8.6) MUO: 57.3 (± 8.7)	Normal weight (<25 kg/m2) Obesity (≥25 kg/m2)	≥ 1 Cardiometabolic abnormalities	MHNW: 337/12150 MUNW: 149/4469 MHO: 181/6014 MUO: 721/20966	Cancer registry	MHNW: Reference MUNW: 2.12 (1.19–3.80) MHO: 1.24 (0.99–1.55) MUO: 1.59 (1.30–1.96	Age at baseline, race, education, age at menarche, breastfeeding history, age at first live birth, parity, hormone replacement therapy, oral contraceptive use, menopausal status at baseline, sister age at diagnosis of breast cancer, smoking history, alcohol consumption, and physical activity
Park, 2021	South Korea	8 years	3,095,336	All participants were aged ≥ 40 years at baseline were incluyed People who have aged >80 years, those with missing information and those who had availed healthcare services for any type of cancer or catastrophic illness before or within 6 months from the date of health examination were excluded.	MHNW: 59.5 (± 8.2) MUNW: 64 (± 8.2) MHO: 60.6 (± 7.6) MUO: 63.1 (± 7.8)	Normal weight (<25 kg/m2) Obesity (≥25 kg/m2)	ATP III	MHNW: 10996/1505754 MUNW: 4709/552612 MHO: 2753/430046 MUO: 5126/606924	Cancer registry	MHNW: Reference MUNW: 1.25 (1.21–1.30) MHO: 1.05 (1.01–1.10) MUO: 1.37 (1.32–1.42)	Age, age at menarche, age at menopause, hormone replacement therapy use after menopause, delivery, duration of breastfeeding, oral contraceptive use, family history of any cancer, drinking frequency per week during the last 1 year, smoking, and physical activity including vigorous physical activity, moderate physical activity, and walking per week.
Kabat, 2017	USA	15 years	20,944	All participants were aged 50 to 79 years at baseline were incluyed. People with diabetes reported at baseline, with missing information and women with a history of breast cancer were excluyed.	MHNW: 64.8 (± 7.5) MUNW: 66.9 (± 6.5) MHO: 63.2 (± 7.2) MUO: 63.4 (± 7.0)	Normal weight (<25 kg/m2) Overweigt (25 - 29.99 kg/m2) Obesity (≥ 30 kg/m2)	ATP III	MHNW: 219/4585 MUNW: 28/675 MHO: 202/3347 MUO: 345/4902	Cancer registry	MHNW: Reference MUNW: 0.86 (0.51–1.38) MHO: 1.31 (1.07–1.61) MUO: 1.61 (1.34–1.94)	Age, smoking status, pack-years of smoking, alcohol intake, physical activity, age at first birth, age at menarche, age at menopause, oral contraceptives, hormone therapy, parous/nulliparous, family history of breast cancer in first-degree relative, history of breast biopsy, breastfed for more than 6 months, education, ethnicity
Sun, 2023	Europe	40 years	397 082	People with missing information, with extreme values of height, weight or BMI; BMI less than 18.5 kg/m2; mismatching dates; or a prevalent cancer (excluding carcinoma in situ and basaliomas) were excluyed.	42.8 (± 9.1)	Normal weight (<25 kg/m2) Overweigt (25 - 29.99 kg/m2) Obesity (≥ 30 kg/m2)	The top tertile of the metabolic score	MHNW: 145302/2644 MUNW: 48154/1113 MHO: 9873/229 MUO: 24916/664	Cancer registry	MHNW: Reference MUNW: 1.04 (0.96 to 1.13) MHO: 1.13 (0.97 to 1.31) MUO: 1.08 (0.99 to 1.18)	Baseline age and smoking

Tabla 2: Evaluación De La Calidad De Los Estudios Incluidos Mediante La Escala Newcastle-Ottawa Para Estudios De Cohorte

Authors, year	Selection				Comparatibility		Outcome				
	Representativenes of the exposed cohort	Selection of the non-exposed cohort	Exposure Ascertainment	Outcome not present at the start of the study	Study controls for sex and age	Study controls for any additional important factor	Assement of outcome	Length of follow-up	Adequacy of follow up	Score	Overall Judgement
Gunter, 2015	*	*	*	*	*	*	*	*	*	9	Low risk
Park, 2017	*	*	*	*	*	*	*	*	*	9	Low risk
Kabat, 2017	*	*	*	*	*	*	*	*	*	9	Low risk
Park, 2017	*	*	*	*	*	*	*	*	*	9	Low risk
Sun, 2023	*	*	*	*	*		*	*	*	8	Low risk

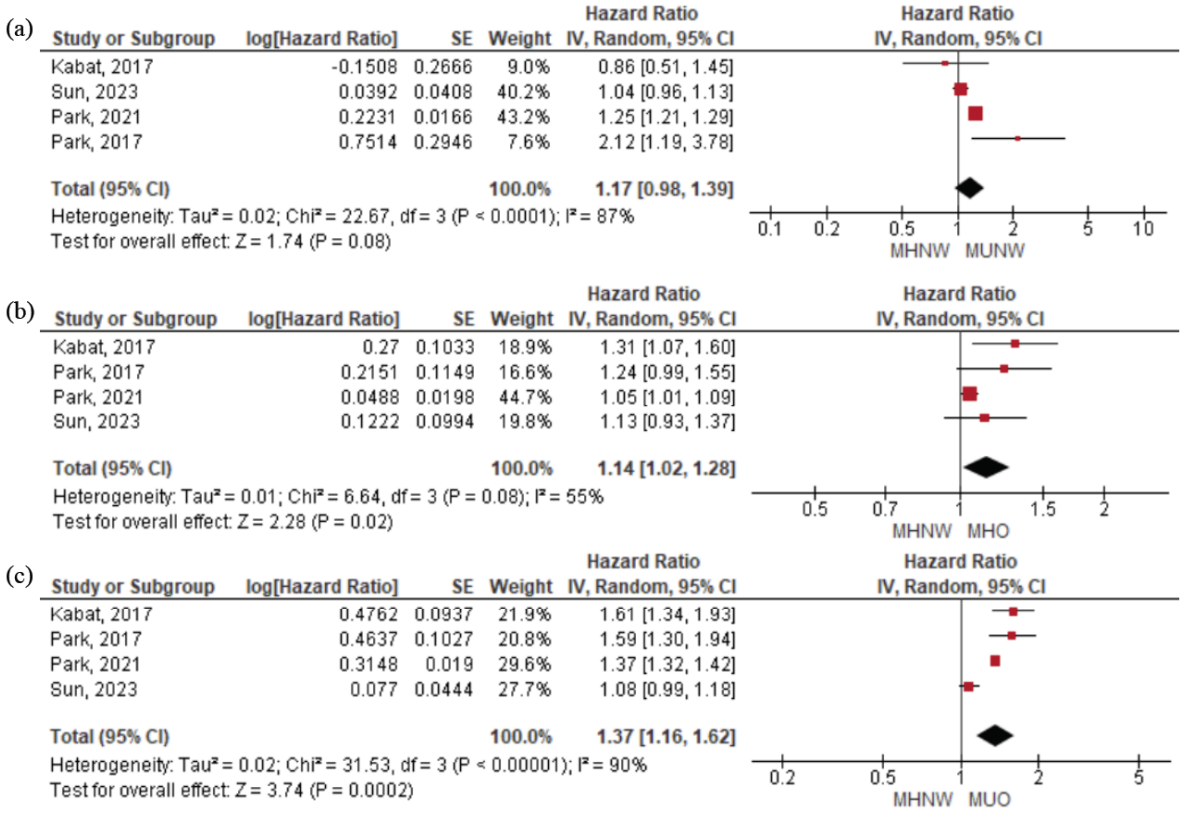

Figura 2: Meta-analysis for the association of MUNW (**a**), MHO (**b**) and MUO (**c**) phenotype, compared with individuals with MHNW.

Meta-Analysis of the Association between Metabolically Unhealthy States and Breast Cancer

For the meta-analysis, only studies that used HR as an association measure and evaluated the states of MHNW, MUNW, MHO, and MUO were included. It was found that, compared to individuals with MHNW, there was a statistically significant association between the development of BC and the MHO state (HR: 1.14; 95% CI 1.02, 1.28) and the MUO state (HR: 1.37; 95% CI 1.16, 1.62). No association was found with the MUNW state. Heterogeneity, measured through I2, ranged from 55% to 90%. As only Kabat *et al*. [10] and Sun *et al*. [12] were considered overweight, they were not included in the meta-analysis.

DISCUSSION

The SR assessed the relationship between metabolic phenotypes and BC, utilizing a substantial

dataset derived from various populations. These cohort studies were conducted in the United States, South Korea, and Europe, spanning a follow-up period of 6.4 to 40 years. This geographical and temporal diversity is a notable strength of the review, as it enables comparison of results across different contexts and over time.

There was variation in the criteria used to define the unhealthy metabolic state across the studies. The ATPIII criteria provides a solid basis for participant classification and has been widely used in previous research to refer to metabolic alterations [18]. However, the study that classified individuals as metabolically unhealthy if they had one or more cardiometabolic abnormalities might be less rigorous. It could also allow for the early identification of at-risk individuals [13]. Finally, the study by Sun M *et al*. [12], which used the upper tertile of the metabolic score, might allow for a more nuanced risk assessment. However, it may also be more susceptible to variations among populations. Each approach has its merits and limitations, and the choice of criteria can influence the observed results. Therefore, it is important to consider these differences when interpreting the findings in the meta-analysis.

While these findings support a link between MUO and BC, substantial heterogeneity among studies indicates uncertainty. Differences in the definitions used for metabolic phenotypes and incomplete adjustment for some important confounders may have contributed to the observed heterogeneity. Additionally, most studies were conducted in Western white populations, necessitating further research to confirm these associations in other populations.

Furthermore, it is important to highlight that using a few studies for the meta-analysis may also limit the generalizability of the results. Given the variability in population characteristics, measurement methods, and confounding factors in different studies and contexts, these findings may not apply to all populations. Additionally, including only two investigations could increase the risk of publication bias, as studies that do not find a significant association are less likely to be published. Nonetheless, this limitation underscores the need for more research in this field. More studies are needed to confirm our findings and explore the relationship between metabolic phenotypes and BC risk in different contexts and populations. Future research could also benefit from using standardized methods for measuring metabolic phenotypes and assessing potential confounding factors.

Interpretation of Results

A crucial aspect of this systematic review is the significant impact of obesity on BC risk. Our findings indicate that obesity, measured by BMI, constitutes an important risk factor independent of the underlying metabolic state. Although an altered state can increase this risk, obesity alone is important. This observation is particularly relevant as lean individuals with metabolic alterations did not show a significant increase in BC risk, suggesting that obesity plays an independent role in promoting this cancer.

The relationship between obesity and increased BC risk has been widely recognized. Overweight or obese women have a higher risk of being diagnosed with BC compared to those who maintain a healthy weight, especially after menopause. Moreover, overweight may also increase the risk of BC recurrence in women who have already had the disease [19].

Obesity is recognized as a leading modifiable risk factor for the development of BC; however, this association varies considerably depending on clinicopathological characteristics, and the underlying mechanisms are complex [20]. Obesity-associated inflammation is strongly linked to BC risk and progression, largely through inflammatory pathways and dysregulated metabolism. Producing cytokines in excess adipose tissue creates a chronic inflammatory microenvironment, favoring tumor development [21].

Pathophysiological Mechanisms

The relationship between metabolic phenotypes and BC, particularly in obese patients, is based on the interaction of multiple metabolic and biological factors. These include increased systemic inflammation, lipid and glucose metabolism dysfunction, and hormonal signaling pathway changes.

Obesity promotes a chronic inflammatory state by releasing pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha by adipose tissue [22–24]. This chronic inflammation can induce DNA damage and alter normal cell function, increasing the risk of mutations and cancer development.

High insulin and blood glucose levels, common in insulin resistance (IR) states, can promote cell

proliferation and tumorigenesis Hyperinsulinemia can activate insulin-like growth factor-1 (IGF-1), which plays a role in cell proliferation and survival [25,26]. Also, IR can lead to increased estrogen production, a known risk factor for BC. Dyslipidemia, another common feature in individuals with MUO, can also contribute to cancer pathogenesis [27,28].

Another pathophysiological approach would be related to adiposity levels.Adipose tissue in individuals with obesity can become a reservoir for estrogen production, stimulating breast cell proliferation and promoting tumorigenesis. Additionally, this disease can result in an imbalance in the production of adipokines and cytokines that affect cell proliferation and apoptosis [29].

Additionally, obesity is associated with mitochondrial dysfunction and elevated levels of reactive oxygen species (ROS), which can damage cells and Deoxyribonucleic Acid (DNA), increasing cancer risk. Excess visceral fat appears to promote chronic systemic oxidative stress. Hypertrophic adipocytes in obese individuals show altered mitochondrial respiration, reduced ATP production, and increased ROS release. These ROS can cause mutations and genomic rearrangements, contributing to neoplastic transformation and activating signaling pathways that promote uncontrolled cell proliferation and evasion of apoptosis [30,31].

Public Health Importance

With the rising prevalence of obesity and metabolic disorders, an increase in BC incidence is anticipated in the coming decades. It is essential to implement effective preventive measures. Early identification of women with obesity offers a crucial opportunity to focus preventive strategies on diet modification, exercise, and weight loss to reduce BC incidence significantly.

Understanding the specific mechanisms through which metabolically healthy and unhealthy states in obesity promote BC is key to developing new prevention and treatment strategies. This could include new screening modalities and pharmacological therapies to reduce insulin resistance, systemic inflammation, and oxidative stress, which are key risk factors in obesity.

Raising awareness among women and healthcare professionals about the relationship between obesity and BC is vital. This could motivate patients to adopt and maintain lifestyle-centered prevention strategies, especially those at high risk. Additionally, in these women, more intensive monitoring, including more frequent screening mammograms, may be justified for early and effective BC detection.

Study Limitations

First, the selected studies may have variations in populations, breast cancer diagnostic methods, and definitions of metabolic states, which could affect the generalization of the results. Second, there was flexibility in defining metabolic states and criteria for classifying normal weight, overweight, and obesity. This variability could influence the consistency of findings and their interpretation. Third, although the NCO bias assessment tool was used, differences in the quality and design of the included studies could have influenced the results; some studies, for example, controlled for only a limited number of confounding variables.

Fourth, the significant heterogeneity among the selected studies (I2 ranging from 55% to 90%) suggests variability in results, which could affect the validity of the meta-analysis conclusions. Additionally, including a limited number of studies in the meta-analysis may limit the robustness of the findings. Finally, there is always a risk of publication bias, where studies with positive or significant results are more likely to be published than those with negative or non-significant results.

CONCLUSIONS

Our study indicates that obesity, as determined by BMI, is significantly associated with an increased risk of breast cancer, regardless of metabolic status. Furthermore, UM states, especially in obese individuals, appear to increase the risk of breast cancer. The biological mechanisms involved include systemic inflammation, metabolic dysfunction, altered production of hormones such as estrogen, and oxidative stress related to mitochondrial dysfunction.

Given these findings, it is crucial to focus on obesity prevention and control as a key strategy to reduce breast cancer risk. This includes promoting healthy lifestyles, such as a balanced diet and regular exercise. Additionally, it is recommended to conduct long-term longitudinal studies to better understand the temporal relationship between metabolic phenotypes and breast cancer risk. These studies should control for a wide

range of confounding variables to provide a clearer understanding of the associations between the study variables. Finally, future meta-analyses should aim to include a larger number of studies to enhance the robustness and reliability of the presented findings.

ACKNOWLEDGMENTS

A special thanks to the members of the Tropical Diseases Research Institute, Universidad Nacional Toribio Rodríguez de Mendoza de Amazonas (UNTRM), Amazonas, Peru, for their support and contributions throughout the completion of this research.

FINANCIAL DISCLOSURE

This study is self-financed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT

It was not necessary to obtain informed consent in this Study

DATA AVAILABILITY

Data are available upon request to the corresponding author.

AUTHORS' CONTRIBUTION

Víctor Juan Vera-Ponce: Conceptualization, Investigation, Methodology, Resources, Project administration, Writing - Original Draft, Writing - Review & Editino.

Joan A. Loayza-Castro: Software, Data Curation, Formal analysis, Writing - Review & Editino.

Luisa Erika Milagros Vásquez Romero: Validation, Visualization, Writing - Original Draft, Writing - Review & Editino.

Fiorella E. Zuzunaga-Montoya: Methodology, Supervision, Funding acquisition, Writing - Review & Editino.

REFERENCES

[1] Cancer today [Internet]. [citado el 11 de junio de 2023]. Disponible en: http://gco.iarc.fr/today/home

[2] Rakha EA, Tan PH, Quinn C, Provenzano E, Shaaban AM, Deb R, *et al*. UK recommendations for HER2 assessment in breast cancer: an update. J Clin Pathol 2023; 76(4): 217-27. https://doi.org/10.1136/jcp-2022-208632

[3] Cáncer de mama [Internet]. [citado el 11 de junio de 2023]. Disponible en: https://www.who.int/es/news-room/fact-sheets/detail/breast-cancer

[4] Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, *et al*. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin 2018; 68(1): 31-54. https://doi.org/10.3322/caac.21440

[5] DeSantis CE, Miller KD, Goding Sauer A, Jemal A, Siegel RL. Cancer statistics for African Americans, 2019. CA Cancer J Clin 2019; 69(3): 211-33. https://doi.org/10.3322/caac.21555

[6] Amadou A, Ferrari P, Muwonge R, Moskal A, Biessy C, Romieu I, *et al*. Overweight, obesity and risk of premenopausal breast cancer according to ethnicity: a systematic review and dose-response meta-analysis. Obes Rev 2013; 14(8): 665-78. https://doi.org/10.1111/obr.12028

[7] Peruchet-Noray L, Dimou N, Sedlmeier AM, Fervers B, Romieu I, Viallon V, *et al*. Body Shape Phenotypes and Breast Cancer Risk: A Mendelian Randomization Analysis. Cancers (Basel) 2023; 15(4): 1296. https://doi.org/10.3390/cancers15041296

[8] Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Doosti Irani A. Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. PLoS One 2012; 7(12): e51446. https://doi.org/10.1371/journal.pone.0051446

[9] Park Y-MM, White AJ, Nichols HB, O'Brien KM, Weinberg CR, Sandler DP. The association between metabolic health, obesity phenotype and the risk of breast cancer. Int J Cancer 2017; 140(12): 2657-66. https://doi.org/10.1002/ijc.30684

[10] Kabat GC, Kim MY, Lee JS, Ho GY, Going SB, Beebe-Dimmer J, *et al*. Metabolic Obesity Phenotypes and Risk of Breast Cancer in Postmenopausal Women. Cancer Epidemiol Biomarkers Prev 2017; 26(12): 1730-5. https://doi.org/10.1158/1055-9965.EPI-17-0495

[11] Park B, Kim S, Kim H, Cha C, Chung MS. Associations between obesity, metabolic health, and the risk of breast cancer in East Asian women. Br J Cancer 2021; 125(12): 1718-25. https://doi.org/10.1038/s41416-021-01540-5

[12] Sun M, Fritz J, Häggström C, Bjørge T, Nagel G, Manjer J, *et al*. Metabolically (un)healthy obesity and risk of obesity-related cancers: a pooled study. J Natl Cancer Inst 2023; 115(4): 456-67. https://doi.org/10.1093/jnci/djad008

[13] Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, *et al*. The Obese Without Cardiometabolic Risk Factor Clustering and the Normal Weight With Cardiometabolic Risk Factor Clustering: Prevalence and Correlates of 2 Phenotypes Among the US Population (NHANES 1999-2004). Arch Intern Med 2008; 168(15): 1617-24. https://doi.org/10.1001/archinte.168.15.1617

[14] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6(7): e1000097. https://doi.org/10.1371/journal.pmed.1000097

[15] Ottawa Hospital Research Institute [Internet]. [citado el 11 de julio de 2022]. Disponible en: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

[16] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21(11): 1539-58. https://doi.org/10.1002/sim.1186

[17] Cochrane Handbook for Systematic Reviews of Interventions [Internet]. [citado el 27 de noviembre de 2021]. Disponible en: https://training.cochrane.org/handbook

[18] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285(19): 2486-97. https://doi.org/10.1001/jama.285.19.2486

[19] Excess Weight and Breast Cancer: What's the Risk? [Internet]. [citado el 17 de diciembre de 2023]. Disponible en: https://www.breastcancer.org/risk/risk-factors/being-overweight

[20] Naaman SC, Shen S, Zeytinoglu M, Iyengar NM. Obesity and Breast Cancer Risk: The Oncogenic Implications of Metabolic Dysregulation. J Clin Endocrinol Metab 2022; 107(8): 2154-66. https://doi.org/10.1210/clinem/dgac241

[21] Seiler A, Chen MA, Brown RL, Fagundes CP. Obesity, Dietary Factors, Nutrition, and Breast Cancer Risk. Curr Breast Cancer Rep 2018; 10(1): 14-27. https://doi.org/10.1007/s12609-018-0264-0

[22] Zhang K, Chen L, Zheng H, Zeng Y. Cytokines secreted from adipose tissues mediate tumor proliferation and metastasis in triple negative breast cancer. BMC Cancer 2022; 22(1): 886. https://doi.org/10.1186/s12885-022-09959-6

[23] Hildebrandt X, Ibrahim M, Peltzer N. Cell death and inflammation during obesity: "Know my methods, WAT(son)". Cell Death Differ 2023; 30(2): 279-92. https://doi.org/10.1038/s41418-022-01062-4

[24] Kern L, Mittenbühler MJ, Vesting AJ, Ostermann AL, Wunderlich CM, Wunderlich FT. Obesity-Induced TNFα and IL-6 Signaling: The Missing Link between Obesity and Inflammation-Driven Liver and Colorectal Cancers. Cancers (Basel) 2018; 11(1): 24. https://doi.org/10.3390/cancers11010024

[25] Gallagher EJ, LeRoith D. Hyperinsulinaemia in cancer. Nat Rev Cancer 2020; 20(11): 629-44. https://doi.org/10.1038/s41568-020-0295-5

[26] Zhang AMY, Wellberg EA, Kopp JL, Johnson JD. Hyperinsulinemia in Obesity, Inflammation, and Cancer. Diabetes Metab J 2021; 45(3): 285-311. https://doi.org/10.4093/dmj.2020.0250

[27] Bhardwaj P, Brown KA. Obese Adipose Tissue as a Driver of Breast Cancer Growth and Development: Update and Emerging Evidence. Front Oncol 2021; 11: 638918. https://doi.org/10.3389/fonc.2021.638918

[28] Mair KM, Gaw R, MacLean MR. Obesity, estrogens and adipose tissue dysfunction - implications for pulmonary arterial hypertension. Pulm Circ 2020; 10(3): 2045894020952019. https://doi.org/10.1177/2045894020952023

[29] Gérard C, Brown KA. Obesity and breast cancer - Role of estrogens and the molecular underpinnings of aromatase regulation in breast adipose tissue. Mol Cell Endocrinol 2018; 466: 15-30. https://doi.org/10.1016/j.mce.2017.09.014

[30] Avagliano A, Ruocco MR, Aliotta F, Belviso I, Accurso A, Masone S, *et al*. Mitochondrial Flexibility of Breast Cancers: A Growth Advantage and a Therapeutic Opportunity. Cells 2019; 8(5): 401. https://doi.org/10.3390/cells8050401

[31] Brown KA. Metabolic pathways in obesity-related breast cancer. Nat Rev Endocrinol 2021; 17(6): 350-63. https://doi.org/10.1038/s41574-021-00487-0

Received on 10-06-2024 Accepted on 09-07-2024 Published on 01-08-2024

https://doi.org/10.6000/1929-6029.2024.13.09