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Abstract: 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: A 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
(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/m\(^2\), 25–29.9 kg/m\(^2\), and ≥30 kg/m\(^2\) 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/m\(^2\)) versus overweight/obesity (≥25 kg/m\(^2\)).

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.

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Figure 1: Flowchart.
<table>
<thead>
<tr>
<th>First Author, year</th>
<th>Country</th>
<th>Follow up time (mean or median)</th>
<th>Sample</th>
<th>Population (selection criteria)</th>
<th>Age at cohort entry</th>
<th>Definition of normal weight, overweight and obesity</th>
<th>Definition of metabolic unhealthy</th>
<th>Incidence of breast cancer (%)</th>
<th>Breast cancer ascertainment</th>
<th>Association measure</th>
<th>Adjustment variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park, 2017</td>
<td>USA</td>
<td>6.4 years</td>
<td>43,599</td>
<td>People who have aged 25 to 64 years were included. People who had incomplete information, have unclear menopausal status, pregnant, breastfeeding, who were overweight or who had a history of any cancer except non-melanoma skin cancer were excluded.</td>
<td>MHNW: 53 (± 8.0) MUNW: 60.2 (± 8.2) MHO: 53.4 (± 8.6) MUO: 57.3 (± 8.7)</td>
<td>Normal weight (&lt;25 kg/m²)</td>
<td>Obesity (≥25 kg/m²)</td>
<td>≥ 1 Cardiometabolic abnormalities</td>
<td>MHNW: 337/15150 MUNW: 1494469 MHO: 1316014 MUO: 72120966</td>
<td>Cancer registry</td>
<td>Age at baseline, race, education, age at menarche, breastfeeding, 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</td>
</tr>
<tr>
<td>Park, 2021</td>
<td>South Korea</td>
<td>8 years</td>
<td>3,095,336</td>
<td>All participants were aged ≥40 years at baseline were included. People who have aged &gt;80 years, those with missing information and those who had availed healthcare services for any type of cancer or catastrophic illnesses before or within 6 months from the date of health examination were excluded.</td>
<td>MHNW: 55.5 (± 8.2) MUNW: 64 (± 8.2) MHO: 60.6 (± 7.6) MUO: 63.1 (± 7.8)</td>
<td>Normal weight (&lt;25 kg/m²)</td>
<td>Obesity (≥25 kg/m²)</td>
<td></td>
<td>MHNW: 10668/1505754 MUNW: 4709/652612 MHO: 2754340046 MUO: 5126/606924</td>
<td>Cancer registry</td>
<td>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</td>
</tr>
<tr>
<td>Kabat, 2017</td>
<td>USA</td>
<td>15 years</td>
<td>20,944</td>
<td>All participants were aged 50 to 79 years at baseline were included. People with diabetes reported at baseline, with missing information and women with a history of breast cancer were excluded.</td>
<td>MHNW: 64.8 (± 7.5) MUNW: 66.9 (± 6.5) MHO: 63.2 (± 7.2) MUO: 63.4 (± 7.0)</td>
<td>Normal weight (&lt;25 kg/m²)</td>
<td>Overweight (25 - 29.99 kg/m²) Obesity (≥30 kg/m²)</td>
<td>ATP III</td>
<td>MHNW: 21944585 MUNW: 284675 MHO: 2222347 MUO: 3545802</td>
<td>Cancer registry</td>
<td>Age, smoking status, pack-years of smoking, alcohol intake, physical activity, age at firstbirth, 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</td>
</tr>
<tr>
<td>Sun, 2023</td>
<td>Europe</td>
<td>40 years</td>
<td>397,082</td>
<td>People with missing information, with extreme values of height, weight or BMI: BMI less than 18.5 kg/m²; mismatching dates; a prevalent cancer (excluding carcinoma in situ and basalomas) were excluded.</td>
<td>42.8 (± 9.1)</td>
<td>Normal weight (&lt;25 kg/m²)</td>
<td>Overweight (25 - 29.99 kg/m²) Obesity (≥30 kg/m²)</td>
<td>The top tertile of the metabolic score</td>
<td>MHNW: 145302/2644 MUNW: 481541113 MHO: 9733229 MUO: 24916/664</td>
<td>Cancer registry</td>
<td>Age at baseline and smoking</td>
</tr>
</tbody>
</table>
Tabla 2: Evaluación De La Calidad De Los Estudios Incluidos Mediante La Escala Newcastle-Ottawa Para Estudios De Cohorte

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Representativeness of the exposed cohort</th>
<th>Selection of the non-exposed cohort</th>
<th>Exposure ascertainment</th>
<th>Outcome not present at the start of the study</th>
<th>Study controls for sex and age</th>
<th>Study controls for any additional important factor</th>
<th>Assesment of outcome</th>
<th>Length of follow-up</th>
<th>Adequacy of follow up</th>
<th>Score</th>
<th>Overall Judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gunter, 2015</td>
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<td>Low risk</td>
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<td>Park, 2017</td>
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<td>Low risk</td>
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<td>Kabat, 2017</td>
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<td>Low risk</td>
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<td>Park, 2017</td>
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<td>Low risk</td>
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<tr>
<td>Sun, 2023</td>
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<td>Low risk</td>
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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**

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**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**

Victor 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: https://goi.iarc.fr/today/home


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