From humans to canines: Unraveling the impact of metabolic health on mammary cancer across species

De humanos a caninos: Desentrañando el impacto de la salud metabólica en el cáncer de mama entre especies

De humanos a caninos: Desvendando o impacto da saúde metabólica no câncer de mama entre espécies

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Abstract

The relationship between metabolic health and breast cancer emerges as an expanding area of research in comparative oncology, particularly highlighted in studies conducted among humans and canines. This review explores how dietary habits, obesity, and metabolic syndromes influence the risk, progression, and response to breast cancer treatments. To this end, the impact of obesity, diet, and lifestyle on carcinogenesis mechanisms and prognosis in human and canine patients affected by mammary tumors is examined. By examining comparative studies addressing the relationship between metabolic health and breast cancer in women and canines, common molecular and biochemical pathways in both species are identified. This approach provides a broader understanding of oncological diseases and their development, suggesting potential strategies for the prevention, diagnosis, and treatment of breast cancer from a metabolic perspective. However, as this area of research is still developing, it is necessary to explore new research lines to fully understand the complex relationship between metabolic health and cancer across different species from biochemical, molecular, genetic, and epigenetic perspectives, with the goal of gaining valuable knowledge that contributes to the development of new diagnostic, prognostic, and therapeutic tools.

Keywords: *Biomarkers; breast cancer; canine mammary tumor; comparative oncology; diet and lifestyle; insulin resistance; metabolic health; obesity.*

Resumen

La relación entre la salud metabólica y el cáncer de mama emerge como un área en expansión en la oncología comparativa, destacada especialmente en estudios realizados entre humanos y caninos. Esta revisión explora cómo los hábitos dietéticos, la obesidad y los síndromes metabólicos influyen en el riesgo, la progresión y la respuesta a los tratamientos contra el cáncer de mama. Con este fin, se examina el impacto de la obesidad, la dieta y el estilo de vida en los mecanismos de carcinogénesis y el pronóstico en pacientes humanos y caninos

afectados por tumores mamarios. Al revisar estudios comparativos que abordan la relación entre la salud metabólica y el cáncer de mama en mujeres y caninos, se identifican vías moleculares y bioquímicas comunes en ambas especies. Este enfoque proporciona una comprensión más amplia de las enfermedades oncológicas y su desarrollo, sugiriendo estrategias potenciales para la prevención, el diagnóstico y el tratamiento del cáncer de mama desde una perspectiva metabólica. Sin embargo, dado que esta área de investigación está en desarrollo, es necesario explorar nuevas líneas de investigación para comprender completamente la compleja relación entre la salud metabólica y el cáncer en diferentes especies desde perspectivas bioquímicas, moleculares, genéticas y epigenéticas, con el objetivo de obtener conocimientos valiosos que contribuyan al desarrollo de nuevas herramientas diagnósticas, pronósticas y terapéuticas.

Palabras clave: *Biomarcadores; cáncer de mama; dieta y estilo de vida; obesidad; oncología comparativa; resistencia a la insulina; salud metabólica; tumor mamario canino.*

Resumo

A relação entre saúde metabólica e câncer de mama emerge como uma área em expansão na oncologia comparativa, especialmente destacada em estudos conduzidos entre humanos e caninos. Esta revisão explora como hábitos alimentares, obesidade e síndromes metabólicas influenciam o risco, a progressão e a resposta aos tratamentos contra o câncer de mama. Para isso, examina-se o impacto da obesidade, da dieta e do estilo de vida nos mecanismos de carcinogênese e no prognóstico em pacientes humanos e caninos afetados por tumores mamários. Ao examinar estudos comparativos que abordam a relação entre saúde metabólica e câncer de mama em mulheres e caninos, são identificadas vias moleculares e bioquímicas comuns em ambas as espécies. Este enfoque proporciona uma compreensão mais ampla das doenças oncológicas e seu desenvolvimento, sugerindo estratégias potenciais para a prevenção, diagnóstico e tratamento do câncer de mama sob uma perspectiva metabólica. No entanto, dado que esta área de pesquisa ainda está em desenvolvimento, é necessário explorar novas linhas de pesquisa para compreender completamente a complexa relação entre saúde metabólica e câncer em diferentes espécies a partir de perspectivas bioquímicas, moleculares,

genéticas e epigenéticas, com o objetivo de obter conhecimentos valiosos que contribuam para o desenvolvimento de novas ferramentas de diagnóstico, prognóstico e terapêuticas.

Palavras-chave: *Biomarcadores; câncer de mama; dieta e estilo de vida; obesidade; oncologia comparativa; resistência à insulina; saúde metabólica; tumor mamário canino.*

Introduction

In the dynamic domain of oncology, the intricate relationship between metabolic health and mammary cancer across species, particularly in women and canines, prompts a reassessment of conventional cancer care strategies. This review merges insights from evolving breast cancer research in women with studies in canine mammary cancer, depiction on comparative oncological studies to highlight overlap and translational benefits. With recent literature as a basis, we explore into the complex interplay of diet, obesity, and metabolic syndromes, examining their impact on mammary cancer risk, progression, and therapeutic outcomes. Initially, we discuss the role of metabolic health in breast cancer among women, examining how factors like obesity, diet, and insulin resistance influence disease outcomes. Shifting focus to canine mammary cancer, we explore how similar factors affect tumor development and progression in dogs, enriching our understanding of the disease in veterinary medicine. By offering a comparative analysis between human and canine mammary cancer, this review aims to uncover shared pathways and therapeutic targets, advancing diagnostic and treatment approaches in both fields. Through this approach, we emphasize the significance of a more holistic and cross-disciplinary approach to cancer research, emphasizing the importance of understanding the impact of metabolic health on mammary cancer to develop more effective and personalized therapeutic strategies.

Metabolic health and breast cancer in women

Metabolic Health and Breast Cancer Risk

Metabolic health profoundly impacts breast cancer in multiple ways, nonetheless current research has unveiled complexities that warrant critical examination. For instance, although the potential therapeutic implications arising from comprehending estrogen receptor activity in metabolic balance are intriguing, their clinical translation remains unclear (Mahboobifard

et al., 2022). The link between insulin resistance and aggressive breast cancer underscores the importance for comprehensive management strategies, although the effectiveness of existing approaches requires more examination (Guinan *et al*., 2013). The significant influence of adipocytes on breast cancer progression highlights the necessity of addressing obesity-related factors. In particular, breast cancer promotes the dedifferentiation of adjacent adipocytes into cancer-associated adipocytes, which secrete cytokines and adipokines, facilitating tumorigenesis and metastasis through mechanisms like ECM remodeling and metabolic reprogramming (Wu *et al*., 2023). However, the efficacy of interventions targeting adipose tissue remains variable. While weight-reducing lifestyle interventions improve adipose tissue function and lower breast cancer risk, adherence, and long-term sustainability are challenging (Bhardwaj & Brown, 2021). Comprehensive metabolic evaluations beyond Body Mass Index (BMI), such as measures of insulin resistance, adipokine profiles, and inflammatory markers, are advocated for assessing breast cancer risk. Nevertheless, the practical implementation and impact on clinical decision-making are still to be fully elucidated (Feigelson *et al*., 2021; Naaman *et al*., 2022).

Indeed, while metabolic health profoundly impacts breast cancer risk and outcomes, the mechanistic underpinnings linking obesity and type 2 diabetes to distinguish susceptibility through insulin, inflammation, and adipose dysfunction require further elucidation (Sankofi *et al*., 2023). Managing fasting blood glucose and waist circumference is emphasized for prevention, but the optimal thresholds and the true impact on risk reduction require clarification (Haseen *et al*., 2015; Park *et al*., 2021). Additionally, understanding metabolic alterations such as the Warburg effect is crucial, although translating this knowledge into effective therapeutic strategies remains challenging (Pereira *et al*., 2022). Tailored prevention strategies for postmenopausal women are proposed, though their comparative efficacy against broader population-based approaches requires more investigation (Park *et al*., 2017). The complex interplay between metabolic syndrome and breast cancer characteristics needs further exploration, particularly regarding its implications for personalized treatment approaches (Motoki *et al*., 2022). For instance, IGF-1 signaling is involved in 87% of invasive breast cancer patients, supporting cancer progression and therapy resistance, which leads to decreased survival in HER2-positive cases. Additionally, higher IGF-1/IGFBP-3 ratios are linked to poorer outcomes in overweight patients (Tong *et al*., 2020). While obesity

is recognized as a modifiable risk factor, the specific mechanisms through which dysfunctional adipose tissue, insulin signaling, and chronic inflammation contribute to tumorigenesis need deeper investigation (Andò *et al*., 2020; Nehme *et al*., 2022).

Although research suggests a correlation between abnormal metabolic markers and increased breast cancer risk, the clinical utility of these markers, particularly in guiding risk stratification and treatment decisions, remains unclear (Melvin *et al*., 2017). Similarly, while elevated serum glucose levels correlate with poorer breast cancer prognosis, the causal relationship and implications for treatment remain unclear (Melvin *et al*., 2017; Ahmed *et al*., 2023). The imperative of tight glycemic control in diabetic breast cancer patients underscores the need for further investigation into its impact on outcomes and survival (Ahmed *et al*., 2023). A complex interplay between metabolic health and breast cancer risk is observed, highlighting the importance of continued research to better understand these relationships and their implications for the diagnosis and treatment of breast cancer.

Obesity in Breast Cancer

A critical examination is necessary to explore the profound impact of obesity on breast cancer. While tumor-associated macrophages (TAMs), notably M2 macrophages abundant in the breast cancer microenvironment, are influenced by obesity, the precise mechanisms and their clinical significance remain unclear. Although recognition exists that obesity upregulates estrogen production via *CYP19* gene transcription, further investigation is necessary to determine the extent to which this contributes to adverse breast cancer outcomes and the potential for targeted interventions (Rosendahl *et al*., 2018). Additionally, despite being metabolically healthy, obese women still face elevated risks of obesity-associated cancer mortality, suggesting underlying complexities beyond traditional metabolic markers. The impact of obesity on breast cancer varies with menopausal status and subtype, highlighting the need for varied approaches to risk assessment and management (Picon-Ruiz *et al*., 2017; Brantley *et al*., 2022). Metabolites related to BMI offer insights into breast carcinogenesis, nonetheless the specific pathways connecting BMI and breast cancer risk require further elucidation. Dysregulated steroid hormone metabolism and branched-chain amino acid metabolism are implicated, but their precise roles in mediating obesity-related breast cancer risks remain incompletely understood (Moore *et al*., 2018). Similarly, the

interaction between obesity and adipocytes influences breast cancer initiation, progression, and metastasis, but the intricate molecular mechanisms driving these processes demand deeper investigation (Balaban *et al*., 2017; Chu *et al*., 2019). Hormonal imbalances, particularly elevated estrogen levels, are implicated, however the potential for targeted interventions remains an area of ongoing research (Zhong *et al*., 2023). In summary, the impact of obesity on breast cancer involves a complex interplay of molecular, immune, and metabolic mechanisms that require further investigation. While studies have identified associations between obesity and breast cancer risks and outcomes, further research is needed to fully elucidate the underlying pathways and potential therapeutic targets. Additionally, the implications of obesity-induced inflammation on immune responses and treatment outcomes underscore the need for comprehensive understanding and targeted interventions in managing obesity-related breast cancer risks (Nguyen *et al*., 2023).

Biomarkers and Metabolomics in Breast Cancer

In the realm of biomarkers and metabolomics in breast cancer, while potential biomarkers show promise for diagnostic, predictive, and therapeutic applications, a critical evaluation is warranted to assess their clinical utility and validity (Table 1). Iron deposits within TAMs and PI3K inhibitors are highlighted for their potential insights into immunotherapy responses and therapy monitoring, but their clinical validation and translation into practice require further scrutiny (Moestue *et al*., 2013; Leftin *et al*., 2019). Serum metabolomics have revealed potential predictive biomarkers for trastuzumab response in HER2-positive breast cancer, however their robustness and reproducibility across diverse patient populations remain to be confirmed (Mao *et al*., 2022). Associations between insulin resistance, hyperglycemia, and breast cancer progression underscore the need for comprehensive understanding and targeted interventions, although translating these findings into clinical practice poses challenges (Durrani *et al*., 2021; Ahmed *et al*., 2023). The association between the 21-gene recurrence score (RS) and metabolic factors emphasizes the potential prognostic value of RS in ER-positive, HER2-negative early-stage breast cancer, but its integration into routine clinical practice requires further investigation (Zhu *et al*., 2021). In conclusion, various studies highlight the complex interplay between metabolic factors, biomarkers, and

breast cancer risk, emphasizing the need for personalized approaches and deeper investigation.

Table 1. Metabolic Health Biomarkers in Human Breast Cancer.

Biomarker	Impact	Potential Applications	Reference
Insulin resistance	Linked to breast cancer aggressiveness	Management during prevention, diagnosis, and treatment	De Santi *et al*., 2023; Guinan *et al*., 2013
Adiponectin	Low levels associated with higher risk	Target for obesity-related interventions	Andò *et al.*, 2020; Nehme *et al*., 2022
Leptin	High levels promote cancer progression	Target for obesity-related interventions	Taroeno-Hariadi *et al*., 2021
Resistin	Facilitates breast cancer progression	Prognostic marker	Patrício *et al*., 2018
Fasting blood glucose	High levels associated with increased risk	Risk assessment and management	Park *et al*., 2021; Haseen *et al*., 2015
Waist circumference	Indicator of central obesity linked to higher risk	Risk assessment and lifestyle interventions	Park *et al*., 2021; Lynch *et al*., 2010
Body Mass Index	High BMI linked to increased risk, especially in postmenopausal women	Risk assessment and lifestyle interventions	Moore *et al*., 2018; Feigelson *et al*., 2021
Estrogen receptor activity	Estrogen promotes tumor growth	Therapeutic target	Mahboobifard *et al*., 2022
Fibroblast growth factor receptors	Involved in adipose tissue dysfunction	Therapeutic target	Sankofi *et al*., 2023
PI3K/AKT/mTOR pathway	Involved in cell growth, metabolism, and survival	Therapy monitoring	Moestue *et al*., 2013
Iron Deposits within TAM	Metabolic marker of tumor microenvironment.	Biomarkers for predicting immunotherapy responses.	Leftin *et al*., 2019

Metabolic health and canine mammary cancer

Obesity and Canine mammary cancer

The intricate association between obesity and canine mammary tumors (CMTs) provides valuable insights into obesity-related cancer risks, drawing comparisons to human contexts. However, while obesity significantly influences CMT onset and progression, our understanding of the underlying mechanisms remains incomplete and call for critical evaluation (Lim *et al*., 2015a, Lim *et al*., 2015b; Marchi *et al*., 2022). Associations between leptin, its receptor (ObR), and tumor characteristics suggest potential roles in signaling pathways, nevertheless further investigation is necessary to elucidate the exact mechanisms involved (Lim *et al*., 2015a). Additionally, while obesity correlates with increased risks of various tumors, including transitional cell carcinoma and mammary gland tumors, the specific contributions of hormonal and adipokine pathways require more detailed examination (Queiroga *et al*., 2005; Marchi *et al*., 2022). Lim *et al*. (2015) highlight lower ages of CMT onset and higher-grade tumors in overweight or obese dogs, underscoring the need to explore additional factors beyond body condition score (BCS) in CMT development (Lim *et al*., 2015a). Elevated counts of TAMs in overweight or obese dogs suggest a potential link between obesity-induced inflammation and CMT progression, although the precise mechanisms remain uncertain (Lim *et al*., 2022). While serum resistin concentrations correlate with tumor aggressiveness and obesity in female dogs with CMTs, the clinical utility of resistin as a prognostic marker requires further validation (Nicchio *et al*., 2020). Chronic inflammation triggered by obesity may impact aromatase expression and cancer progression, but more comprehensive studies are needed to establish clear parallels with human breast cancer (Shin *et al*., 2016). Addressing these knowledge gaps through further research is essential for the development of targeted interventions in veterinary oncology.

Metabolic health markers in canine mammary cancer

A review of biomarkers in CMTs underscores their potential as models for human breast cancer (HBC), offering insights into shared epidemiological and histopathological characteristics (Table 2). Elevated serum IL-6 and IL-8 levels in malignant CMTs suggest IL-6 and IL-8 as diagnostic biomarkers, highlighting their importance in prognosis (Ren *et al*., 2023). Reduced klotho expression links to tumor progression, advocating klotho as a

prognostic factor (Chung *et al*., 2022). The presence of CD204-positive TAMs in CMTs indicates M2-polarized macrophage infiltration as a prognostic biomarker, reflecting on tumor aggressiveness (Seung *et al*., 2018). Metabolic reprogramming in CMTs parallels human breast cancer, with potential biomarkers in carbohydrate, lipid metabolism, and plasma-free amino acids, suggesting opportunities for targeted therapy (Marchi *et al*., 2022; Tamarindo *et al*., 2023). The impact of obesity on insulin resistance and mammary tumor risks underscores the role of hormones and adipokines as prognostic markers, urging further exploration in both veterinary and human oncology (Marchi *et al*., 2022). These findings accentuate the importance of CMTs in biomarker research, requiring continued investigation to enhance diagnostic and therapeutic strategies in both canine and human oncology.

Table 2. Metabolic Health Biomarkers in Canine Mammary Cancer.

Biomarker	**Impact**	**Potential Applications**	**Reference**
Adiponectin	Low levels associated with aggressive tumor behavior	Target for obesity-related interventions	Lim *et al*., 2015a; Marchi *et al*., 2022
Leptin	Associated with tumor characteristics, independent of body condition	Target for intervention	Queiroga *et al*., 2005; Marchi *et al*., 2022
Body condition score (BCS)	Obesity linked to early tumor development and progression	Risk assessment and management in veterinary practice	Lim *et al*., 2015a
Macrophage infiltration in tumor microenviroment	Indicates a pro-inflammatory state associated with high-grade tumors	Prognostic indicator and therapeutic target	Seung *et al*., 2018
Aromatase expression	Higher in overweight/obese dogs, involved in hormone-related tumor growth	Therapeutic target in CMT	Lim *et al*., 2015a; Shin *et al*., 2016
Resistin	Hyperresistinemia related to tumor aggressiveness and obesity	Prognostic marker in CMT	Nicchio *et al*., 2020
Insulin resistance	Contributes to mammary tumor risks	Risk assessment	Marchi *et al*., 2022

IL-6 and IL-8	Pro-inflammatory cytokine associated with tumor progression	Target for immunomodulatory therapy	Irac *et al*., 2019; Ren *et al*., 2023

Metabolic health and comparative studies between human and canine mammary cancer

Persistent challenges in human breast cancer research have encouraged the exploration of alternative translational models, such as CMT, which exhibit promising parallels with human breast cancer. Despite a lower mutational burden, CMTs share prevalence, molecular subtypes, and histological traits with HBC, providing valuable insights through comparative studies (Abdelmegeed *et al*., 2018; Kwon *et al*., 2023). Molecular similarities, including steroid receptor expression and mutations in genes like *TP53*, underscore the relevance of canine models in comparative oncology, offering potential avenues for understanding common signaling pathways and mutations. Challenges persist in HER2 detection, but epigenetic studies propose diagnostic biomarkers like LINE-1 hypomethylation (Bergholtz *et al*., 2022; Oh *et al*., 2023). Comparative analyses delineate intrinsic molecular subtype similarities and distinctions, providing insights into personalized treatments and highlighting the modeling potential of CMTs (Bergholtz *et al*., 2022). Cytokine associations in CMTs mirror those in HBC, suggesting potential prognostic markers and therapeutic targets (Irac *et al*., 2019). Hormone-related aspects, such as low ERα and PR expression in CMCs, parallel risks in HBC, emphasizing the preclinical research potential of canine models (Nguyen *et al*., 2018). Comparative microRNA expression studies uncover shared genetic characteristics and regulatory mechanisms, offering promising avenues for therapy development. Recent research highlights the roles of miR-21 and miR-29b in both human and canine mammary tumors. Elevated levels of miR-21 serve as a biomarker that can differentiate clinically healthy dogs from those with mammary tumors. Furthermore, in breast cancer, elevated miR-21 levels correlate with a worse prognosis. On the other hand, miR-29b, which regulates cell proliferation and metastasis, shows promise as a non-invasive biomarker for both cancers. Notably, miR-29b is overexpressed in human breast cancer cells as well as in the canine mammary gland tumor SNP cell line (Gherman *et al*., 2024). Understanding miRNA-mediated regulation holds promise for targeted therapies, showcasing the translational impact of comparative oncology in advancing treatments for HBC (Sahabi *et al*., 2018).

Furthermore, the utilization of canine mammary cancer as a translational model for human breast cancer has broadened our comprehension of cancer and potential therapeutic approaches. Comparative analyses, exemplified by REM-134 RR cell lines, have unearthed mechanisms of radioresistance, unveiling parallel pathways (Gray *et al*., 2020). Additionally, the establishment of living biobanks housing CMT organoids provides valuable insights into tumor biology and treatment outcomes, serving as a platform for preclinical drug assays (Inglebert *et al*., 2022). Despite inherent differences, CMT models, especially those with PIK3CA mutations in ER+ tumors, exhibit promise in evaluating antiestrogen compounds and combatting therapy resistance. These comparative investigations shed light on shared biological traits and prognostic markers, thereby advancing therapeutic approaches for breast cancer across species.

This review was conducted with the objective of comparing breast cancer in women and mammary cancer in dogs, specifically examining the interplay of diet, obesity, and metabolic syndromes on cancer risk, progression, and therapeutic outcomes. This interdisciplinary approach aims to elucidate shared pathways and therapeutic targets between the two species. By integrating insights from evolving research in both fields, this work seeks to advance understanding of how factors such as obesity, diet, and insulin resistance influence the development and course of mammary cancer. Through this comparative analysis, the study intends to foster translational benefits, ultimately contributing to more effective and personalized diagnostic and therapeutic strategies for both human and veterinary patients with mammary cancer.

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Conflicts of interest

The authors declare no conflicts of interest regarding the publication of this paper.

Author contributions

William F. Osorio-Zambrano was responsible for conducting the literature review and drafting the manuscript. Fabián D. López-Valbuena undertook the literature review and adapted the manuscript to conform to the format of the RCCP journal. Luis M. Montoya-Flórez performed the stylistic correction of the manuscript.

Use of artificial intelligence (AI)

We used artificial intelligence (AI) technology (ChatGPT-4) during the preparation of this work solely for the purposes of ensuring correct English grammar, searching for scientific articles, and organizing the references. After using ChatGPT-4, we meticulously reviewed and edited the content. We take full responsibility for the content of this publication.

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