IMPACTO CIENTÍFICO EDITORA

SYSTEMATIC REVIEW: INTERMITTENT FASTING AS AN ADJUVANT STRATEGY IN METASTATIC TRIPLE NEGATIVE BREAST CANCER

REVISÃO SISTEMÁTICA: JEJUM INTERMITENTE COMO ESTRATÉGIA ADJUVANTE NO CÂNCER DE MAMA TRIPLO NEGATIVO METASTÁTICO

REVISIÓN SISTEMÁTICA: AYUNO INTERMITENTE COMO ESTRATEGIA ADYUVANTE EN EL CÁNCER DE MAMA METASTÁSICO TRIPLE NEGATIVO

https://doi.org/10.56238/edimpacto2025.087-004

Marina Werner[1]

ABSTRACT

Triple-negative breast cancer (TNBC) is the most aggressive subtype of the disease, marked by high recurrence rates and limited therapeutic response, especially in metastatic stages. In this context, adjunctive strategies such as intermittent fasting and the fasting-mimicking diet (FMD) have gained attention due to their potential effects on tumor progression, metabolic modulation, and reduction of treatment-related toxicity. This systematic review analyzed seven relevant studies, including experimental, clinical, and review articles, assessing the impact of fasting on TNBC management. Findings indicate potential benefits, such as decreased inflammation, increased tumor sensitivity to conventional therapies, and reduced damage to normal cells, although human data remain limited. In conclusion, intermittent fasting and FMD emerge as promising yet experimental strategies, and further well-designed clinical trials are required to establish their efficacy and safety in patients with metastatic TNBC.

Keywords: Advanced Breast Neoplasms. Fasting-Mimicking Diet. Adjunctive Therapies. Tumor Resistance.

RESUMO

O câncer de mama triplo negativo (CMTN) representa o subtipo mais agressivo da doença, com altas taxas de recidiva e resistência terapêutica, sobretudo nos casos metastáticos. Diante disso, estratégias adjuvantes, como o jejum intermitente e a dieta que mimetiza o jejum (FMD), têm despertado crescente interesse por seus potenciais efeitos sobre a progressão tumoral, a modulação metabólica e a redução da toxicidade associada ao tratamento. Esta revisão sistemática reuniu sete estudos relevantes, incluindo experimentais, clínicos e revisões de literatura, que avaliaram o impacto do jejum no manejo do CMTN. Os resultados apontam para benefícios potenciais, como redução da inflamação, sensibilização tumoral a terapias convencionais e menor agressão a células normais, ainda que os dados em humanos sejam incipientes. Conclui-se que o jejum intermitente e a FMD

[1] Master in Development and Society. Universidade do Oeste de Santa Catarina (UNOESC).
E-mail: marina.werner@unoesc.edu.br Orcid: https://orcid.org/0000-0001-6821-2729
Lattes: http://lattes.cnpq.br/2236153820001379

despontam como estratégias promissoras, mas ainda experimentais, sendo necessários ensaios clínicos robustos que confirmem sua eficácia e segurança em pacientes com CMTN metastático.

Palavras-chave: Câncer de Mama Avançado. Dieta Mimetizadora do Jejum. Estratégias Adjuvantes. Resistência Tumoral.

RESUMEN

El cáncer de mama triple negativo (CMTN) representa el subtipo más agresivo de la enfermedad, con altas tasas de recurrencia y resistencia terapéutica, especialmente en casos metastásicos. Por lo tanto, las estrategias adyuvantes, como el ayuno intermitente y la dieta que imita el ayuno (DMF), han generado un creciente interés debido a sus posibles efectos sobre la progresión tumoral, la modulación metabólica y la reducción de la toxicidad asociada al tratamiento. Esta revisión sistemática reunió siete estudios relevantes, incluyendo revisiones experimentales, clínicas y bibliográficas, que evaluaron el impacto del ayuno en el manejo del CMTN. Los resultados apuntan a posibles beneficios, como la reducción de la inflamación, la sensibilización tumoral a las terapias convencionales y la reducción del daño a las células normales, aunque aún se carece de datos en humanos. Concluimos que el ayuno intermitente y la DMF emergen como estrategias prometedoras, pero aún son experimentales, requiriendo ensayos clínicos sólidos para confirmar su eficacia y seguridad en pacientes con CMTN metastásico.

Palabras clave: Cáncer de Mama Avanzado. Dieta Que Simula el Ayuno. Estrategias Adyuvantes. Resistencia Tumoral.

1 INTRODUCTION

Breast cancer is characterized by the disordered multiplication of breast cells, which start to become abnormal and divide continuously, forming a tumor. It is a heterogeneous disease, as it has different subtypes, each with its own characteristics that influence its evolution and aggressiveness. While some types develop rapidly, others grow more slowly, requiring different diagnostic and treatment strategies. Although it is more common in women, breast cancer can also affect men, although it represents only about 1% of all registered cases. (INCA, 2025).

Breast cancer is the most frequent type among women, second only to non-melanoma skin cancer. For 2025, the National Cancer Institute (INCA) estimates that 73,610 new cases of the disease will be diagnosed in women in Brazil. Mortality data are also significant: in 2021, 18,361 deaths from the disease were recorded, 18,139 in women and 220 in men, according to the Atlas of Cancer Mortality. These numbers reinforce the relevance of breast cancer as a serious public health problem and the need for effective prevention, early diagnosis, and timely treatment strategies (INCA, 2025).

Triple-negative breast cancer (TNBC) is recognized as the most aggressive subtype of breast cancer, with high clinical aggressiveness and a higher probability of recurrence compared to the other subtypes (Bianchini et al., 2016). The introduction, in recent years, of therapeutic regimens that combine chemotherapy and immunotherapy, both in the neoadjuvant context for localized disease and in metastatic cases, has contributed to advances in the prognosis of patients at different stages (Cortes et al., 2020; Schmid et al., 2018, 2020). Even so, the clinical outcome of most women with advanced-stage TNMC remains unfavorable, due to primary or acquired tumor resistance to available treatments, as well as the presence of tumor stem cells (CSCs), which favor neoplastic repopulation after an initial positive response (Charafe-Jauffret et al., 2009).

In recent years, different experimental studies have pointed out that fasting cycles or fasting-mimicking diets (FMD), defined by significant calorie restriction (equal to or greater than 50%), associated with low protein and carbohydrate content and higher lipid intake, can potentiate the response to conventional therapies in various types of cancer, including breast cancer. In addition to favoring the efficacy of treatments, these strategies seem to confer a protective effect on healthy cells, reducing the intensity of toxicities associated with chemotherapy (Brandhorst et al., 2015; Caffa et al., 2020; Di Biase et al., 2016; Di Tano et al., 2020; Lee et al., 2010, 2012; Long; Mattson, 2014; Raffaghello et al., 2008; Salvadori et al., 2022). This benefit is related, in part, to the decrease in serum levels of IGF-1, glucose,

leptin, and insulin, which modulate in a differentiated way the expression of genes involved in cellular defense processes, such as DNA repair and antioxidant activity.

In the specific case of triple-negative breast cancer (TNBC), interventions based on the association between FMD and chemotherapy demonstrated a reduction in tumor progression, but without a consistent impact on long-term progression-free survival. In addition, less damage to normal cells was observed, although not completely eliminated (Di Biase et al., 2016; Lee et al., 2012; Salvadori et al., 2022). Considering that cancer stem cells (CSCs) play a central role in tumor initiation, maintenance, and resistance, recent investigations have sought to understand how FMD can interfere with the survival of these cells and, consequently, with the evolution of TNBC and the response to targeted therapies.

In view of the clinical and scientific relevance of the topic, the general objective of this article was to perform a narrative review on triple-negative breast cancer (TNBC) and the current evidence on the use of intermittent fasting and the fasting-mimicking diet (FMD) as adjuvant therapeutic strategies. Experimental and clinical studies were gathered that point to the potential of these interventions in reducing tumor progression, increasing the efficacy of conventional therapies, and attenuating treatment-related adverse effects.

2 METHODOLOGY

Systematic review is a structured scientific method that aims to identify, select, critically evaluate, and synthesize the results of relevant studies on a previously defined research question. Unlike narrative reviews, which offer a broader and more interpretative view of the topic, systematic reviews follow strict and transparent protocols, usually based on guidelines such as PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). This approach seeks to minimize biases, increase the reliability of conclusions, and provide more solid evidence for clinical practice, public policy formulation, and the advancement of scientific research (Galvão; Pereira, 2014; Page et al., 2021).

In the context of TNBC and nutritional strategies based on intermittent fasting and fasting-mimicking diet (FMD), conducting a systematic review can significantly contribute to the consolidation of available scientific evidence. This type of approach allows for the careful identification and gathering of preclinical and clinical studies that evaluated the efficacy and safety of these interventions, in addition to enabling a comparative analysis between methodologies, populations investigated, and observed outcomes. Such a process would reduce interpretation biases, providing more robust subsidies to guide clinical practice and direct future research, especially considering the scarcity of large-scale clinical trials in this specific field (Galvão; Pereira, 2014; Page et al., 2021).

To search for studies, the PubMed and SciELO databases were used, selected for their scope and relevance in the health area. PubMed was chosen because it provides a large number of articles indexed in high-impact international journals, while SciELO was included because it brings together Latin American and Brazilian scientific productions, ensuring greater regional representation. The descriptors used in the research were: "triple negative", "metastatic breast cancer", "intermittent fasting" and "breast cancer". The search strategy included combining the terms with Boolean operators, for example: ("triple negative" OR "triple negative") AND ("breast cancer" OR "breast cancer") AND ("metastatic" OR "metastatic") AND ("intermittent fasting" OR "intermittent fasting"). Thus, we sought to expand the sensitivity and specificity of the search, retrieving publications aligned with the objective of the study.

3 RESULTS AND DISCUSSION

The process of selecting the studies followed the steps proposed by the PRISMA flowchart. Initially, 135 articles were identified, 128 of which came from the PubMed and SciELO databases and 7 obtained from other sources. After the exclusion of 22 duplicates, 113 records remained for analysis of titles and abstracts, of which 74 were discarded because they did not meet the proposed theme. Thus, 39 articles were evaluated in full, resulting in the exclusion of 32 studies because they did not present data relevant to the objective of the review. At the end of the process, 7 articles were included that made up the analysis of this review. Table 1 presents the articles selected for the article.

Recent literature points out that intermittent fasting and the fasting-mimicking diet (FMD) may play a relevant role as adjuvant strategies in triple-negative breast cancer (TNMC). The study by Salvadori et al. (2022) demonstrated that FMD cycles reduce the self-renewal capacity of tumor stem cells, delaying tumor progression and increasing survival in animal models. However, the same study warns of the activation of compensatory pathways, such as PI3K/AKT/mTOR, which may favor cellular adaptation, suggesting the need for combined therapies. This observation dialogues directly with the findings of Vernieri et al. (2023), who showed that the association between FMD and immunotherapies potentiated the antitumor response in models of low-immunogenic TNMC. Thus, while Salvadori et al. highlight limitations of FMD alone, Vernieri et al. reinforce its potential when integrated with targeted therapies.

The metabolic impact of these interventions was also analyzed by Gao et al. (2024), who verified the attenuation of tumor progression in obese mice with TNMC submitted to intermittent fasting. The study highlights the interface between obesity, inflammation, and

cancer, suggesting that metabolic intervention can reduce both tumor volume and the inflammatory microenvironment. These results complement those of Salvadori and Vernieri, by reinforcing that fasting can act on multiple fronts: modulating metabolism, drug sensitivity, and immune response.

From a translational point of view, the reviews by Nencioni et al. (2023) and Wilkinson et al. (2023) broaden the understanding by analyzing the molecular mechanisms and clinical safety of fasting in cancer patients. Nencioni et al. report that the combination of fasting with chemo or radiotherapy increases antitumor efficacy in murine models, including TNBC. Wilkinson et al. observed that time-restricted eating (ERT) is safe in cancer patients, although there is still a lack of robust trials that specifically evaluate metastatic TNMC. Taken together, these studies reinforce that, although preclinical data are promising, clinical results remain incipient.

Table 1

Articles selected to compose the review.

Article / Year	Model	Key Findings	Conclusions
1. Salvadori et al., 2022 – *Fasting-mimicking diet blocks TNBC*	Animal and in vitro models (TNBC cells)	FMD reduced tumor stem cell markers, inhibited tumor progression, and prolonged survival in mice. Activation of PI3K-AKT/mTOR pathways in differentiated cells.	FMD may be an adjuvant strategy in TNBC, but it may induce activation of escape pathways → combinations with targeted drugs may be necessary.
2. Vernieri et al., 2023 – *Short-term fasting + immunotherapy*	Murine TNBC models low immunogenic	FMD increased efficacy of immunotherapies (anti-PD-L1, anti-OX40). Reduction of tumor growth and improvement of immune infiltration.	Short fasting or FMD may sensitize TNBC tumors to immunotherapy. Potential for application in resistant patients.
3. Gao et al., 2024 – *Intermittent Fasting Attenuates Obesity-Induced TNBC*	Obese mice with TNBC	IF reduced body weight, tumor volume, inflammation in the tumor microenvironment, cell migration/invasion.	Intermittent fasting may mitigate tumor progression in obesity-associated TNBC. It suggests an interaction between metabolism and cancer.
4. Nencioni et al., 2023 – *Intermittent fasting & cancer* (review)	Preclinical and clinical review	He reports that fasting increases sensitivity to chemotherapy and radiotherapy; in murine TNBC, IF+ radiation was more effective.	Growing but still preliminary evidence in humans.
5. Wilkinson et al., 2023 – *Time-restricted eating in cancer*	Systematic review	Evaluated ERT in cancer patients: improvement of metabolic markers, but limited evidence in TNBC.	TRE seems safe, but robust trials for metastatic TNBC are lacking.

Article / Year	Model	Key Findings	Conclusions
6. Braspen Journal, 2024 – *Fasting and chemotherapy*	Small clinical trials (several tumors, some breast)	Fasting for 18 to 96 hours reduced toxicities (nausea, stomatitis, fatigue). No significant effect on the efficacy of chemotherapy in all studies.	It may be a strategy to reduce adverse effects, but there is no consensus on direct antitumor benefit.
7. Han et al., 2024 – *Decanoylcarnitine & TNBC*	In vitro and animal studies	Metabolic intervention reduced progression and expression of MMP9 in TNBC. Related to fasting-like mechanisms (energy metabolism).	It suggests that metabolic manipulation (such as IF or derivatives) may modulate progression in TNBC.

Source: the author 2025.

In the clinical setting, the study published in the Braspen Journal (2024) systematized trials of intermittent fasting in different types of cancer and identified a reduction in toxicities common to chemotherapy, such as nausea and stomatitis, without, however, demonstrating consistent benefit in survival or tumor response. These findings are similar to those pointed out by Wilkinson et al. (2024) in that both reinforce the safety of fasting as an adjuvant, but highlight the absence of conclusive evidence on a direct impact on cancer outcomes.

Finally, the experimental study by Han et al. (2024), although it did not directly evaluate fasting, investigated metabolic manipulation via decanoylcarnitine in TNBC models, showing a reduction in tumor progression through MMP9 regulation. This study converges with Salvadori et al. and Gao et al. in showing that interventions that affect energy metabolism have the potential to modulate tumor biology in TNBC.

Thus, when correlating the studies, there is a consensus that intermittent fasting and FMD have the potential to reduce tumor progression, modulate metabolic and immunological pathways, and attenuate treatment toxicities, although clinical results are still limited. In a convergent manner, all authors reinforce the need for randomized and larger-scale clinical trials, capable of confirming the efficacy and safety of these strategies, especially in patients with metastatic TNMC.

4 CONCLUSION

Current evidence on intermittent fasting and fasting-mimicking diet (FMD) in triple-negative breast cancer, especially in the metastatic setting, points to a potential adjuvant role of these strategies in cancer treatment. Preclinical studies demonstrate consistent effects, such as reducing tumor progression, decreasing inflammation in the tumor microenvironment, blocking tumor stem cells, and increasing the effectiveness of conventional therapies (chemotherapy, radiotherapy, and immunotherapy). These findings

suggest that fasting may modify central TNBC metabolic pathways (such as PI3K/AKT/mTOR and CDK4/6), as well as modulate the immune response and reduce therapeutic resistance.

In humans, although clinical trials are still limited and heterogeneous, it is observed that controlled periods of fasting can reduce adverse effects of chemotherapy (fatigue, nausea, mucositis), contributing to greater tolerability to treatment. However, there is no robust evidence of a direct impact on survival or tumor reduction in patients with metastatic TNBC, which reinforces the need for caution in extrapolating preclinical data.

It is suggested that more controlled, larger-scale, and well-designed clinical studies be conducted that evaluate not only the efficacy of fasting as an adjunctive therapy, but also its nutritional risks, its impact on quality of life, and its influence on survival outcomes. Only with such evidence will it be possible to consolidate intermittent fasting or FMD as safe and effective strategies in the management of metastatic triple-negative breast cancer.

Therefore, intermittent fasting and FMD emerge as promising, but still experimental, strategies. Its clinical use in patients with metastatic triple-negative breast cancer should be carefully individualized, taking into account the risk of malnutrition, sarcopenia, and cachexia, which are frequent conditions in this group. Larger-scale, controlled clinical trials are needed to validate the safety, efficacy, and applicability of these interventions in the advanced oncological setting.

REFERENCES

Brandhorst, S., [et al.]. (2015). A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. Cell Metabolism, 22(1), 86-99. https://doi.org/10.1016/j.cmet.2015.05.012

Caffa, I., [et al.]. (2020). Fasting-mimicking diet and hormone therapy in breast cancer. Nature Communications, 11, 3515. https://doi.org/10.1038/s41467-020-17239-4

Di Biase, S., [et al.]. (2016). Fasting-mimicking diet reduces HO-1 to promote T cell-mediated tumor cytotoxicity. Cancer Cell, 30(1), 136-146. https://doi.org/10.1016/j.ccell.2016.06.005

Di Tano, M., [et al.]. (2020). Synergistic effect of fasting-mimicking diet and vitamin C against KRAS mutated cancers. Nature Communications, 11, 2332. https://doi.org/10.1038/s41467-020-16243-3

Lee, C., [et al.]. (2010). Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. Science Translational Medicine, 2(26), 26ra27. https://doi.org/10.1126/scitranslmed.3000349

Lee, C., [et al.]. (2012). Fasting or fasting-mimicking diet cycles retard tumor growth and sensitize cancer cells to chemotherapy. Science Translational Medicine, 4(124), 124ra27. https://doi.org/10.1126/scitranslmed.3003293

Ongo, V. D., & Mattson, M. P. (2014). Fasting: Molecular mechanisms and clinical applications. Cell Metabolism, 19(2), 181-192. https://doi.org/10.1016/j.cmet.2013.12.008

Raffaghello, L., [et al.]. (2008). Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. Proceedings of the National Academy of Sciences, 105(24), 8215-8220. https://doi.org/10.1073/pnas.0708100105

Salvadori, G., [et al.]. (2022). Fasting-mimicking diet blocks triple-negative breast cancer and cancer stem cell escape. Cell Reports, 40(7), 111219. https://doi.org/10.1016/j.celrep.2022.111219

Galvão, T. F., & Pereira, M. G. (2014). Revisões sistemáticas da literatura: Passos para sua elaboração. Epidemiologia e Serviços de Saúde, 23(1), 183-184. https://doi.org/10.5123/S1679-49742014000100018

Page, M. J., [et al.]. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ, 372, n71. https://doi.org/10.1136/bmj.n71