International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn24402

Major considerations on the relationship of triple negative breast cancer with microRNAs and nutrological triggers: a systematic review

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DOI: https://doi.org/10.54448/ijn24402

Received: 06-23-2024; Revised: 08-27-2024; Accepted: 09-09-2024; Published: 09-13-2024; IJN-id: e24402

Editor: Dr. Alejandra Giselle Juárez Rebollar, MSc / DDS / OMFS.

Abstract

Introduction: Triple-negative breast cancer (TNBC) accounts for 15% of all cases. Its incidence is usually higher in young women (under 40 years of age). The classification as triple-negative occurs because, in this case, there are no estrogen, progesterone, and HER2 receptors, which are responsible for controlling tumor growth. Higher levels of physical activity and better diet quality are associated with lower mortality from breast cancer in observational studies. Furthermore, physical activity and optimal nutrition can improve the relative dose intensity of chemotherapy, as they can activate miRNAs that regulate several biological processes. **Objective:** This was to conduct a systematic review to establish the main considerations of the relationship between triple-negative breast cancer and microRNAs as biomarkers and regulators of gene expression in cancer cells, as well as to show some nutritional triggers of microRNA activation desirable for breast cancer control. **Methods:** The PRISMA Platform systematic review rules were followed. The search was conducted from April to June 2024 in the Web of Science, Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE and AMSTAR-2 instrument and the risk of bias was analyzed appropriately. According to the Cochrane instrument. **Results and Conclusion:** 112 articles were found, and 40 were evaluated in full and included in this article, 22 of which were included in the systematic review. Considering the Cochrane tool for risk of bias, the global assessment resulted in 15 studies with a high risk of bias and 25 studies that did not reach GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=81.5%>50%. It was concluded that an increasing number of studies have shown that non-coding RNA (ncRNA), including microRNA (miRNA) and long non-coding RNA (lncRNA), play a significant role in tumorigenesis. Although a diet and exercise intervention did not affect relative dose intensity, the intervention was associated with a higher pCR in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative and triple-negative breast cancer undergoing neoadjuvant chemotherapy. High expression levels of miR-27a/b, miR-210, and miR-454 were associated with shorter overall survival, whereas high expression levels of miR-454 and miR-374a/b were associated with disease-free survival. The miRNAs associated with triple-negative breast cancer may provide new avenues for early diagnosis and treatment of breast cancer. Furthermore, specific miRNAs may serve as potential prognostic biomarkers in triple-negative breast cancer.

Keywords: Triple-negative breast cancer. microRNAs. Nutrology. Biomarkers. Gene modulation.

Introduction

In the biological classification, which defines the presence of proteins called hormone receptors (estrogen and/or progesterone) and HER2 protein, there are 4 subtypes: Luminal A and B, HER2, and triple-negative. Triple-negative breast cancer (TNBC)

accounts for 15% of all cases. Its incidence tends to be higher in young women (under 40 years old), Latinas, and black women. It is also more common in women who have mutations in the BRCA1 and/or BRCA2 genes **[1,2]**.

The genes (BRCA1/BRCA2) are hereditary and responsible for protecting the body from the appearance of tumors; when they undergo mutation, this function decreases, and the chances of developing cancer increase. Therefore, when a family member has this mutation, annual medical monitoring of family members is necessary. Of all cases of hereditary breast cancer, 5 to 7% are related to mutations in the BRCA1/BRCA2 genes **[1-3]**.

Unlike other invasive cancers, triple-negative cancer is considered one of the most aggressive, as the cancer cells grow and multiply rapidly, with a greater chance of reappearing in other parts of the body, causing metastasis. The classification as triple-negative occurs because, in this case, there are no estrogen, progesterone, and HER2 receptors, which are responsible for controlling tumor growth, breast cells, and cell division. Hormone receptors are proteins located on the surface of each cell; when hormones bind to these receptors, malignant cells multiply. In triple-negative breast cancer, there is no expression of the HER2 protein or estrogen and progesterone receptors **[3-5]**.

In breast cancer, the presence of receptors allows for more treatment options in addition to chemotherapy. In the case of triple-negative breast cancer, the lack of receptors means that treatment is based on chemotherapy and, in very specific cases, immunotherapy. Triple-negative breast cancer (as well as other subtypes of breast cancer) is diagnosed by biopsy, in which a small portion of the breast nodule is removed for more detailed analysis in the laboratory and pathology. Based on this study, there are two types of reports: anatomopathological and immunohistochemical **[5,6]**.

In this scenario, advances in chemotherapy have contributed to a decrease in mortality in women with early-stage breast cancer. Relative dose intensity (RDI), a measure of chemotherapy completion, is the ratio of the amount of chemotherapy administered versus the amount initially prescribed, considering dose intensity and duration of medication **[7-10]**. Higher levels of physical activity (PA) and better diet quality are associated with lower breast cancer mortality in observational studies **[11-13]**. This is hypothesized to occur through improved metabolic and inflammatory biomarkers. Several organizations recommend a healthy diet and aerobic and resistance exercise after completion of cancer treatment. At diagnosis, many patients have low PA levels and suboptimal diets, and treatment often worsens these lifestyle behaviors **[14]**.

Furthermore, PA and optimal nutrition can improve RDI because they can activate miRNAs that regulate several biological processes, such as proliferation, stress responses, cell adhesion, motility, inflammation, cell survival, senescence, and apoptosis, all of which are critical for tumorigenesis. Increasing evidence suggests that abnormal miRNA expression may be of clinical utility, especially in TNBC, which lacks predictive markers and potential therapeutic targets.

Therefore, the present study performed a systematic review to establish the main considerations of the relationship between triple-negative breast cancer and microRNAs as biomarkers and regulators of cancer cell gene expression, as well as to show some nutritional triggers of microRNA activation desirable for breast cancer control.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 07/21/2024. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 07/21/2024.

Search Strategy and Search Sources

The literature search process was carried out from April to June 2024 and developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (MeSH Terms) were used: "Triple-negative breast cancer. microRNAs. Nutrology. Biomarkers. Gene modulation", and using the Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

The quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials, prospective controlled studies, and retrospective observational studies. Low quality of evidence was attributed to case reports, editorials, and brief communications, according

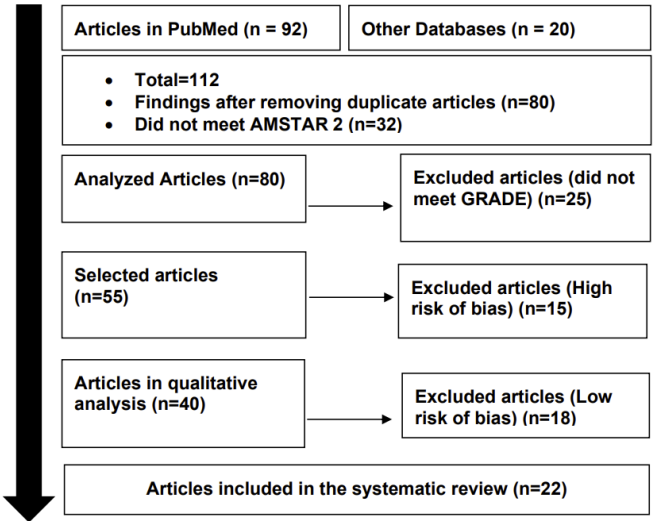
to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

A total of 112 articles were found and submitted to eligibility analysis, with 22 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=81.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 15 studies with a high risk of bias and 25 studies that did not meet GRADE.

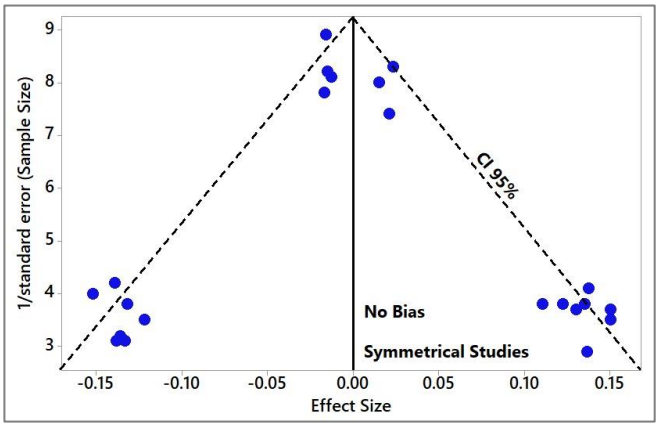
Figure 1. Flowchart showing the article selection process.



Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=22 studies).



Source: Own Authorship.

Main Approaches and Clinical Findings

MiRNAs are small ncRNAs that are typically 18–22 nucleotides in length. The vast majority of all human miRNAs are encoded in introns, exons, intro-exon junctions, or their genes. The process of miRNA biogenesis consists of several stages. First, the miRNA is transcribed as primary miRNA (pri-miRNA) via RNA polymerase II or III. Then it is cut into a hairpin-shaped precursor miRNA (pre-miRNA). Next, the pre-miRNA is transporter-mediated export to the cytoplasm and becomes mature miRNA. Mature miRNA suppresses gene expression by guiding associated proteins to target sites in the 3′ UTR of mRNAs. To date, more than 3000 miRNAs associated with tumor occurrence and progression have been identified (miRbase database). Like lncRNAs, miRNAs can be divided into two categories: oncogenic miRNAs and suppressor miRNAs **[1-4]**.

In this sense, triple-negative breast cancer (TNBC) is currently the most malignant subtype of breast cancer without effective targeted therapies, which makes its pathogenesis an important target for research. A growing number of studies have shown that non-coding RNA (ncRNA), including microRNA (miRNA) and long non-coding RNA (lncRNA), play a significant role in tumorigenesis. Focusing on miRNA and lncRNA associated with TNBC may provide new avenues for early diagnosis and treatment of breast cancer **[15]**.

In this context, the presence of receptors (ER, PR, and HER2) is important to define the best treatment to be performed. Triple-negative breast cancer spreads rapidly. Surgery, quadrantectomy or mastectomy, is an option already in the early stages of the disease to prevent more cells from being affected. In some cases, chemotherapy is chosen to begin to improve the choice of subsequent surgical treatment and to assess the tumor's sensitivity to treatment **[6,7]**.

After surgery, chemotherapy is indicated to prevent the chances of tumor recurrence. In some cases, radiotherapy is also indicated after surgery and chemotherapy. Hormone therapy, the use of medication to inhibit the action of hormones, and anti-HER2 therapy, which controls cell proliferation, are not options for patients with triple-negative breast cancer, as they do not express receptors on their surface **[7,8]**.

In cases of patients with BRCA1/2 mutations, treatment with PARP inhibitors, a class of medications that act on enzymes linked to mutations in BRCA1 and BRCA2, can be used to prevent cell multiplication. In addition, there are options for treating cancer with immunotherapy, when medications are used to stimulate stronger action of the immune system against malignant cells **[9,10]**.

A study conducted by the authors Sanft et al. 2023 **[16]** designed a randomized trial of an exercise and nutrition intervention on relative dose intensity (RDI) and pathologic complete response (pCR) in women diagnosed with breast cancer-initiating chemotherapy. A total of 173 women with stage I-III breast cancer were randomly assigned to usual care (UC, n = 86) or a home-based exercise and nutrition intervention with counseling sessions provided by registered dietitians certified in oncology (n=87). Participants randomly assigned to the intervention had greater improvements in exercise and diet quality compared to UC ($p < 0.05$). RDI was 92.9% ± 12.1% and 93.6% ± 11.1% for intervention and UC, respectively ($p = 0.69$); the proportion of patients in the intervention versus UC who achieved ≥85% RDI was 81% and 85%, respectively ($p = 0.44$). Although a diet and exercise intervention did not affect RDI, the intervention was associated with a higher pCR in patients with hormone receptorpositive/human epidermal growth factor receptor 2-negative and triple-negative breast cancer undergoing neoadjuvant chemotherapy.

Also, the authors Lewis, Jordan, and Tollefsbol (2018) **[17]** evaluated the effects of two epigenetic modifying compounds on markers of growth potential in several triple-negative breast cancer cell lines. Suberoylanilide hydroxamic acid (SAHA), a histone deacetylase (HDAC) inhibitor currently used in the treatment of cutaneous T-cell lymphoma, was administered to triple-negative breast cancer cells alone or in combination with epigallocatechin-3-gallate (EGCG), a DNA methyltransferase (DNMT) inhibitor isolated from green tea. The compounds affected the expression of oncogenic miR-221/222 and tumor suppressors, p27 and PTEN, in addition to estrogen receptor alpha (ERα). E-cadherin expression was increased while N-cadherin was decreased, indicating a more epithelial phenotype. Furthermore, the activity of DNMTs was decreased with the treatments, and there was a significant enrichment of AcH3 within the promoter of p27 and PTEN, suggesting the role of epigenetic mechanisms for the above-mentioned changes. These results translated into reduced migration of triple-negative breast cancer cells with the treatments. In this scenario, epithelial-to-mesenchymal transition (EMT) is highly associated with cancer metastasis. Cyanidin-3-glucoside (C3G), the most abundant anthocyanin pigment enriched in fresh fruits and vegetables, has shown ideal antioxidant properties. C3G can also inhibit certain malignant behaviors of cancer cells, however, whether repression of EMT was involved in its anticancer effect, especially TNBC, remains unknown. C3G was reported to decrease the migratory and invasive nature of TNBC lines MDA-MB-231 and BT-549. C3G induces EMT reversal characterized by phenotype modulation with increased epithelial marker E-ca and ZO-1, decreased mesenchymal marker Vimentin, N-ca, and EMT-associated transcription factors Snail1, Snail2. NF-κB is essential for EMT and Sirt1 is an inhibitor of NF-κB. MicroRNA-138 (miR-138) has been shown to repress Sirt1 via inhibition of mRNA translation and is inhibited by C3G. Furthermore, miR-138 repression is involved in Sirt1 reactivation and migratory and invasive inhibition of TNBC by C3G **[18]**.

In addition, a study developed a miRNA-based approach to reduce telomeric repeat binding factor 2 (TRF2) expression. By performing a high-throughput luciferase screen of 54 candidate miRNAs, miR-182-3p was identified as a specific and efficient post-transcriptional regulator of TRF2. Ectopic expression of miR-182-3p dramatically reduced TRF2 protein levels in a panel of telomerase- or alternative lengthening of telomeres (ALT)-positive cancer cell lines. Furthermore, miR-182-3p induced DNA damage at telomeric and pericentromeric sites, leading to the activation of apoptosis **[19]**.

Besides, EMT, considered an important mechanism by which cancer cells become migratory and invasive, has received increasing attention. Research has shown that miRNAs are involved in the EMT process. Previous studies have identified miR-125b as downregulated in TNBC cells, which is associated with poor prognosis and chemoresistance. It has also been demonstrated that miR-20a could promote tumor initiation and growth, showing the oncogenic function of miRNA during breast tumorigenesis. E-cadherin (CDH1) promotes the formation of adherens junctions and the establishment of polarized cell monolayer, the loss of which is a key event in EMT. In TNBC cells (MDA-MB-231), hsa-miR-20a could control crucial downstream markers, such as CDH1, N-cadherin, and fibronectin, by regulating the expression of Twist-1 mRNA. It has been reported that miRNA-145 regulates tumor cell invasion in TNBC by

targeting adenosine diphosphate (ADP) ribosylation factor 6 (ARF6) **[20,21]**.

Finally, a meta-analysis study by Lü et al. (2017) **[22]** found 21 relevant studies including 2510 individuals were identified. Six miRNAs (miR-155, miR-21, miR-27a/b, miR-374a/b, miR-210, and miR-454) were evaluated in the meta-analysis. Decreased expression of miR-155 was associated with reduced overall survival (adjusted HR = 0.58, 95% CI: 0.34–0.99; crude HR = 0.67, 95% CI: 0.58–0.79). High expression of miR-21 was also predictive of reduced overall survival (crude HR = 2.50, 95% CI: 1.56–4.01). High expression levels of miR-27a/b, miR-210, and miR-454 were associated with shorter overall survival, while high expression levels of miR-454 and miR-374a/b were associated with disease-free survival.

Conclusion

In conclusion, a growing number of studies have shown that noncoding RNA (ncRNA), including microRNA (miRNA) and long noncoding RNA (lncRNA), play a significant role in tumorigenesis. Although a diet and exercise intervention did not affect the relative dose intensity, the intervention was associated with a higher pCR in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative and triple-negative breast cancer undergoing neoadjuvant chemotherapy. High expression levels of miR-27a/b, miR-210, and miR-454 were associated with shorter overall survival, while high expression levels of miR-454 and miR-374a/b were associated with disease-free survival. The miRNAs associated with triple-negative breast cancer may provide new avenues for early diagnosis and treatment of breast cancer. Furthermore, specific miRNAs may serve as potential prognostic biomarkers in triple-negative breast cancer.

CRediT

Author contributions: **Conceptualization -** Márcio do Nascimento Ribeiro, Marla Mayara da Silva Nascimento Ribeiro; **Data curation -** Márcio do Nascimento Ribeiro, Marla Mayara da Silva Nascimento Ribeiro; **Formal Analysis -** Márcio do Nascimento Ribeiro, Marla Mayara da Silva Nascimento Ribeiro; **Investigation -** Márcio do Nascimento Ribeiro, Marla Mayara da Silva Nascimento Ribeiro; **Methodology -** Marla Mayara da Silva Nascimento Ribeiro; **Project administration -** Márcio do Nascimento Ribeiro; **Supervision -** Márcio do Nascimento Ribeiro; **Writing - original draft -** Márcio do Nascimento Ribeiro, Marla Mayara da Silva Nascimento Ribeiro; **Writing-review & editing-** Márcio do Nascimento Ribeiro, Marla Mayara da Silva Nascimento Ribeiro.

Acknowledgment

Not applicable.

Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Funding

Not applicable.

Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Peer Review Process

It was performed.

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