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Role of the microRNA in Prediction of the Breast Cancer

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A B S T R A C T

This paper delves into the ground-breaking role of MicroRNA in forecasting cancer, focusing particularly on breast cancer. MicroRNAs, tiny non-coding RNA molecules, govern gene expression and have surfaced as encouraging biomarkers for cancer prognosis. Traditional approaches to breast cancer forecasting, like mammography and genetic testing, come with constraints in accuracy and sensitivity. MicroRNA-dependent prognostication techniques present benefits, such as stability in bodily fluids, tissue-specific expression patterns, and the potential for non-invasive testing. These techniques can enhance precision, sensitivity, and specificity, resulting in timely detection and personalized treatment plans. Despite the promising outlook for MicroRNA in cancer prognosis, obstacles like standardization of detection techniques and ethical dilemmas require attention. Scopus, PubMed and, Web of Science databases were used, and articles were extracted and reviewed using the keywords microRNA, Breast Cancer, Prediction. The paper concludes that MicroRNA is poised to assume a pivotal role in the timely identification and efficient management of cancer, heralding a new age of tailored medicine.

Keywords: microRNA, Breast Cancer, Prediction

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microRNA and Breast Cancer

Introduction

Understanding breast cancer and the need for accurate prediction methods Breast cancer is one of the most common types of cancer worldwide, affecting millions of women every year. Most breast cancers (85%) are ductal carcinoma – derived from the lining of the mammary ducts. 10% are lobular carcinoma – derived from the mammary lobes – or mixed ductal/lobular carcinoma. Rarer types include mucinous carcinoma (around 2.5% of cases; surrounded by mucin), tubular carcinoma (1.5%; full of small tubes of epithelial cells), medullary carcinoma (1%; resembling "medullary" or middle-layer tissue), and papillary carcinoma (1%; covered in finger-like growths). One of these advances is the discovery of MicroRNA, a small RNA molecule that plays an important role in the regulation of gene expression and has revolutionized cancer prediction (1). Early detection and accurate prediction of breast cancer are essential to improve patient outcomes and increase survival rates. Traditional methods of predicting breast cancer, such as mammography and genetic testing, have limitations in terms of accuracy and sensitivity (2, 3). Mammography, the most common breast cancer screening tool, can miss tumors in dense breast tissue and has a relatively high false positive rate. On the other hand, genetic testing focuses on identifying mutations in specific genes associated with an increased risk of breast cancer. While these tests can provide valuable information, they cannot reveal the complex interplay of various genetic and environmental factors that contribute to the development of breast cancer (4-6) In the field of cancer research, advances in technology and scientific understanding have opened up new opportunities for early detection and accurate prediction of various types of cancer.

MicroRNAs are non-coding RNA molecules that play a role in the post-transcriptional regulation of gene expression. They bind to messenger RNA (mRNA) molecules and break them down or prevent them from being converted into proteins. This regulatory function makes microRNAs useful in maintaining the balance of gene expression and cellular processes (7). microRNA found in plants, animals, and some viruses. Function miRNAs base-pair to complementary sequences in mRNA molecules, leading to gene silencing through cleavage, destabilization, or reduction of translation. Here is a classification of microRNAs based on their roles in promoting or inhibiting progression of different types of breast cancer:

MicroRNAs in Breast Cancer Progression

Table 1. Oncogenic miRNAs (Onco-miRs) (8).

Type of miRNA	Function
miR-21	Upregulated in breast cancer and associated with poor prognosis. Targets tumor suppressor genes like PTEN, PDCD4, and TPM1, promoting cell proliferation, invasion and metastasis
-miR-155	Overexpressed in breast cancer. Regulates genes involved in cell growth, apoptosis and invasion.
miR-10b	Promotes metastasis by targeting HOXD10 and RHOC. Upregulated in invasive breast cancer cells.
miR-373 and miR-520c	Enhance migration and invasion by targeting CD44

Table 2. Tumor Suppressor miRNAs (8)

Type of miRNA	Function
miR-205	Downregulated in breast cancer. Inhibits EMT, migration and invasion by targeting ZEB1/2 and HER3.
- miR-335	Suppresses metastasis by targeting SOX4 and TNC. Often lost in metastatic breast cancer.
miR-31	Inhibits metastasis by targeting RhoA, radixin, integrin-α5, and RDX. Frequently downregulated in metastatic breast tumors
miR-34a	Targets Notch1 and Jagged1, inhibiting breast cancer stem cell properties and metastasis
miR-126 and miR-126	Suppress tumor growth and angiogenesis by targeting IRS-1 and PIK3R2
miR-200 family	Inhibits EMT, invasion and metastasis by targeting ZEB1/2. Downregulated in metastatic breast cancer.

Table 3. MicroRNAs in Breast Cancer Cessation (9, 10).

Type of miRNA	Function
miR-16	Targets cyclin E1 and cyclin J, inhibiting G1/S transition and inducing cell cycle arrest
miR-34a	Targets cyclin D1, leading to G1 cell cycle arrest
miR-449 family	Induces G0/G1 arrest and apoptosis by targeting multiple cell cycle regulators
miR-335	Suppresses proliferation and induces apoptosis by targeting ROCK1 and ROCK2

Types of Breast Cancer

1)Noninvasive (In Situ) Breast Cancers

Ductal Carcinoma in Situ (DCIS)
Develops in the milk ducts and has not spread to nearby tissue or outside the breast
Most common type of noninvasive breast cancer, accounting for 15-20% of all breast cancers
-Lobular Carcinoma in Situ (LCIS)
envelops in the milk-producing lobules and is not considered cancer but increases the risk of developing invasive breast cancer
2)Invasive Breast Cancers
-Invasive Ductal Carcinoma (IDC)
Most common type of invasive breast cancer, accounting for 70-80% of all cases
Starts in the milk ducts and spreads to nearby tissue
-Invasive Lobular Carcinoma (ILC)
Second most common type of invasive breast cancer, accounting for 10-15% of invasive breast cancers
Starts in the milk-producing lobules and spreads to nearby tissue
-Inflammatory Breast Cancer
Rare and aggressive type that occurs in the skin of the breast
Frequently does not have a lump and is often mistaken for an infection
-Paget's Disease of the Nipple
Starts in the nipple and is often accompanied by a rash-like condition around the nipple
-Phyllodes Tumors
Rare tumors that occur in the stroma (connective tissue) of the breast
Can be benign or cancerous
-Angiosarcoma
Rare type that starts in the cells lining the blood vessels or lymph vessels of the breast (11, 12).
These are the main categories of breast cancer, but there are also several less common subtypes, such as medullary, mucinous, tubular, and metaplastic carcinomas. The specific type of breast cancer is determined by examining a sample of the tumor under a microscope and is an important factor in deciding on the best treatment approach.

MicroRNA Transcription and Synthesis in Human Cells

Transcription of miRNA Genes
miRNA genes are primarily transcribed by RNA polymerase II (Pol II), though some are also transcribed by RNA polymerase III (Pol III).
-Pol II-transcribed miRNA genes have promoters near the DNA sequence encoding the hairpin loop of the pre-miRNA.
-The Resulting Pol II transcript is capped, polyadenylated, and spliced, forming a primary miRNA (pri-miRNA) transcript.
-Some miRNA genes are located within the introns or exons of protein-coding genes and are co-transcribed with their host genes (13, 14).
Canonical miRNA Biogenesis Pathway
-The pri-miRNA is cleaved in the nucleus by the microprocessor complex, consisting of the RNase III enzyme Drosha and the double-stranded RNA-binding protein DGCR8 (Pasha in flies), to produce a ~70 nucleotide precursor miRNA (pre-miRNA) hairpin.
-The pre-miRNA is exported from the nucleus to the cytoplasm by the Exportin-5/Ran-GTP complex.
-In the cytoplasm, the pre-miRNA is further cleaved by the RNase III enzyme Dicer, often in complex with the double-stranded RNA-binding protein TRBP, to produce a ~22 nucleotide miRNA: miRNA duplex.
-The miRNA: miRNA duplex is then loaded into an Argonaut (Ago) protein, a core component of the RNA-induced silencing complex (RISC).
-The miRNA strand (the guide strand) is retained in RISC, while the miRNA strand (the passenger strand) is typically degraded (15).
Non-Canonical miRNA Biogenesis Pathways
Some miRNAs bypass one or more steps in the canonical pathway, using alternative mechanisms for their biogenesis.
Examples include Drosha/DGCR8-independent pathways (e.g. mirtrons, snoRNA-derived miRNAs) and Dicer-independent pathways (e.g. miR-451).
The specific mechanisms and factors involved in these non-canonical pathways are still being elucidated.
In summary, the majority of human miRNAs are transcribed by Pol II and undergo the canonical two-step nuclear and cytoplasmic processing to generate mature, functional miRNAs. However, alternative non-canonical pathways also exist that bypass one or more steps in this canonical biogenesis process (16).
The importance of microRNA in predicting breast cancer

microRNA and Breast Cancer

MicroRNAs have emerged as promising biomarkers for breast cancer prediction due to their unique properties. They are stable in body fluids such as blood and urine and can be easily detected and quantified using minimally invasive techniques. In addition, microRNAs exhibit tissue-specific expression patterns, making them ideal candidates for identifying cancer-related changes in gene expression (17, 18). By analyzing the expression levels of specific microRNAs, researchers and clinicians can gain insight into the molecular changes associated with the development and progression of breast cancer. This information can be used to develop more accurate predictive models that take into account the multifactorial nature of breast cancer(19). MicroRNA Processing Mechanisms in Human and Breast Cancer Cells

Role of miRNAs in Breast Cancer

Aberrant expression of miRNAs is associated with many human diseases, including breast cancer.

miRNAs can act as oncogenes (onco-miRs) or tumor suppressors in breast cancer.

Dysregulation of miRNAs in breast cancer is linked to various hallmarks of cancer, such as sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, and induction of angiogenesis. miRNAs can also regulate processes like apoptosis, autophagy, and epithelial-mesenchymal transition (EMT) in breast cancer cells.

In summary, while the majority of human miRNAs undergo the canonical biogenesis pathway, alternative non-canonical pathways also exist. In breast cancer cells, aberrant expression of miRNAs contributes to various aspects of tumor progression and can serve as potential biomarkers and therapeutic targets (20).

Regulation of miRNA Activity

The activity of miRNAs is influenced by various factors, including: Subcellular localization of miRNAs (e.g. nucleus, cytoplasm).

- abundance of miRNAs and their target mRNAs.

-Affinity of miRNA-mRNA interactions.

-Presence of RNA-binding proteins that can modulate miRNA-target interactions (21).

Current methods of breast cancer prediction and their limitations

Although traditional breast cancer prediction methods have been widely used, they have several limitations that hinder their effectiveness. Mammography, as previously mentioned, has limitations in terms of sensitivity and specificity that lead to false positive and false negative results. In addition, mammography is not suitable for women with dense breast tissue, as it can obscure the visibility of tumors (22). Genetic testing, while effective in identifying high-risk individuals with specific gene mutations, cannot capture the full range of genetic and environmental factors that contribute to breast cancer. In addition, genetic testing is often expensive and not easily accessible to everyone, limiting its widespread use as a screening tool (2, 23).

miRNAs sensitivity and specificity in breast cancer

However, microRNAs appear to be more effective in cancer detection due to their sensitivity and specificity .A study identified 30 miRNAs that were dysregulated in breast cancer. An optimized panel of eight miRNAs demonstrated an area under the curve (AUC) of 0.915, with sensitivity at 72.2% and specificity at 91.5% for detecting breast cancer across diverse populations, including pre-malignant lesions and early-stage cancers(24). Another study utilized a support vector machine (SVM) approach to identify a signature of 34 miRNAs, achieving an accuracy of 80.38%, sensitivity of 79%, and specificity of 81% in distinguishing between early and advanced stages of breast cancer (25).

MicroRNA revolution in cancer prediction

Key MicroRNAs Involved in Breast Cancer Progression

Several miRNAs have been identified as playing important roles in the development and progression of breast cancer. Here are some of the main miRNAs specifically involved in breast cancer:

Table 4. Oncogenic miRNAs (Onco-miRs) (26).

Type of miRNA	Function
miR-21	One of the most frequently upregulated miRNAs in breast cancer. It targets tumor suppressor genes like PTEN, PDCD4, and TPM1, promoting cell proliferation, invasion and metastasis.
miR-155	Overexpressed in breast cancer and associated with poor prognosis. It regulates genes involved in cell growth, apoptosis and invasion.
miR-10b	Promotes metastasis by targeting HOXD10 and RHOC. Upregulated in invasive breast cancer cells.
miR-373 and miR-520c	Enhance migration and invasion by targeting CD44.

microRNA and Breast Cancer

Tumor Suppressor miRNAs

These miRNAs regulate various cellular processes like proliferation, apoptosis, EMT, invasion and metastasis in breast cancer. Their dysregulation contributes to breast cancer progression and metastasis. Further research is needed to fully elucidate their clinical applications as biomarkers and therapeutic targets (27, 28).

Table 5. Tumor Suppressor miRNAs

Type of miRNA	Function
miR-205	Downregulated in breast cancer. Inhibits EMT, migration and invasion by targeting ZEB1/2 and HER3.
miR-335	Suppresses metastasis by targeting SOX4 and TNC. Often lost in metastatic breast cancer.
miR-31	Inhibits metastasis by targeting RhoA, radixin, integrin-α5, and RDX. Frequently downregulated in metastatic breast tumors.
miR-34a	Targets Notch1 and Jagged1, inhibiting breast cancer stem cell properties and metastasis
miR-126 and miR-126	Suppress tumor growth and angiogenesis by targeting IRS-1 and PIK3R2
miR-200 family	Inhibits EMT, invasion and metastasis by targeting ZEB1/2. Downregulated in metastatic breast cancer.

Mature MicroRNA Mechanisms in Regulating the Cell Cycle in Breast Cancer

Mature microRNAs (miRNAs) can influence the cell cycle in breast cancer cells through various biochemical mechanisms, including: Targeting Cell Cycle Regulators

-miRNAs can directly target and repress the expression of key cell cycle regulatory proteins, such as cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors.

-For example, miR-34a targets cyclin D1, leading to G1 cell cycle arrest.

-miR-16 targets cyclin E1 and cyclin J, inhibiting G1/S transition.

-miR-7 targets cyclin E1, restoring sensitivity to 5-fluorouracil (29)

Modulating Cell Cycle Checkpoint Pathways

-miRNAs can regulate the expression of genes involved in cell cycle checkpoint pathways, such as the p53 and Rb pathways.

-miR-34a targets p53 inhibitors, activating the p53 pathway and inducing G1 arrest.

-miR-26a targets E2F7, a transcription factor that promotes cell cycle progression, overcoming tamoxifen resistance (30)

Regulating Cell Cycle-Related Transcription Factors

-miRNAs can target transcription factors that control cell cycle genes, such as E2F and FOXM1.

-miR-449 family members target E2F1, E2F3, and CDK2, leading to G0/G1 arrest.

-miR-335 targets FOXM1, a master regulator of the cell cycle, inhibiting proliferation (31).

Influencing Cell Cycle-Related Signaling Pathways

-miRNAs can modulate signaling pathways that regulate the cell cycle, such as the PI3K/Akt and MAPK pathways.

-miR-16 targets FUBP1 and CCNJ, which are involved in the PI3K/Akt pathway, inhibiting proliferation.

-miR-7 targets the EGFR/PI3K/Akt pathway, sensitizing cells to anti-HER2 therapy (32).

Inducing Cell Cycle Arrest and Apoptosis

-Some miRNAs can directly trigger cell cycle arrest and apoptosis in breast cancer cells.

-miR-449 family members induce G0/G1 arrest and apoptosis by targeting multiple cell cycle regulators.

-miR-335 suppresses proliferation and induces apoptosis by targeting ROCK1 and ROCK2 (33).

In summary, mature miRNAs can regulate the cell cycle in breast cancer cells through diverse biochemical mechanisms, including direct targeting of cell cycle regulators, modulation of cell cycle checkpoint pathways, regulation of cell cycle-related transcription factors, and influence on signaling pathways. These miRNA-mediated effects can lead to cell cycle arrest, apoptosis, and altered sensitivity to anti-cancer therapies figure 1.

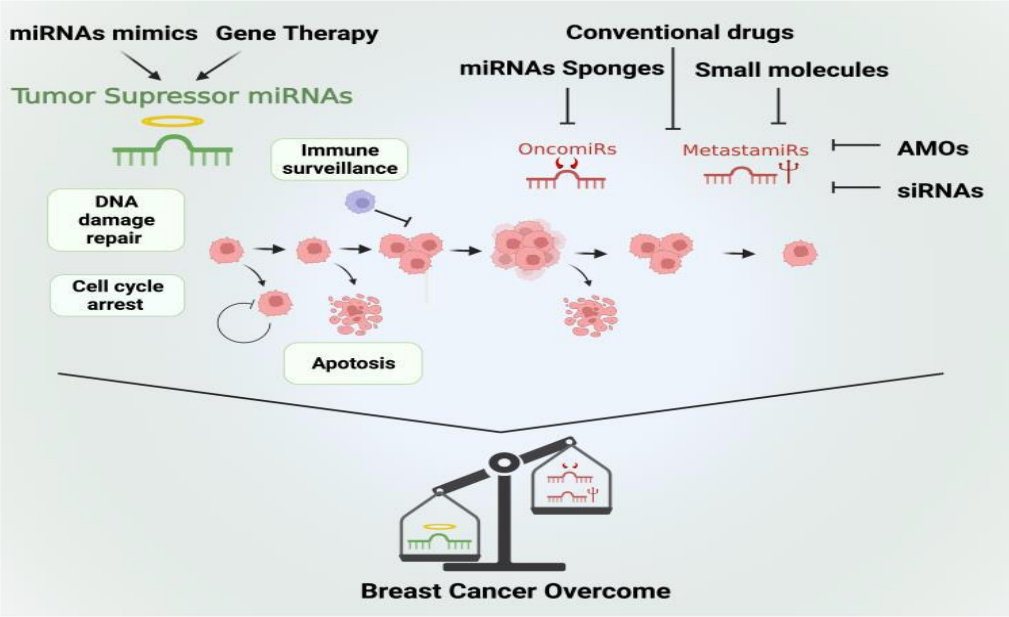

Figure 1. Tumor suppressor miRNAs, oncomiRs, and metastamiRs play critical roles in BC progression. Tumor suppressor miRNAs function to inhibit tumor growth and metastasis by regulating the expression of genes involved in cell cycle control, apoptosis, and DNA repair. These miRNAs are often overexpressed in BC and target tumor suppressor genes. MetastamiRs contribute to the metastatic cascade. They regulate genes involved in cell adhesion, migration, invasion, and angiogenesis, promoting the dissemination of BC cells to distant sites (34).

The discovery of MicroRNA and its role in gene regulation has created a revolution in cancer prediction. Using the unique properties of microRNAs, researchers are developing innovative approaches to accurately predict the development and progression of various types of cancer, including breast cancer (34, 35). MicroRNA-based prediction methods offer several advantages over traditional methods. First, the stability and detectability of microRNAs in body fluids allow for non-invasive and easily accessible testing. This minimizes the discomfort and discomfort associated with traditional screening methods. microRNAs provide valuable insights into the molecular changes underlying cancer development and enable personalized and targeted therapeutic strategies. Finally, microRNA-based predictive models have the potential to improve accuracy, sensitivity, and specificity, and reduce false-positive and false-negative results (36-38).

miRNAs Targeting BRCA1 and BRCA2 in breast cancer

-miR-182 targets BRCA1 and is repressed by ionizing radiation.

-miR-146a and miR-146-5p target BRCA1 and are modulated by diflourinated-curcumin (CDF) and EZH2.

-miR-15a and miR-16 target BRCA1 and are induced by curcumin.

-miR-638 targets BRCA1 and is induced by benzo(a)pyrene (BaP).

-miR-17 targets BRCA1 and is regulated by Myc and Cyclin D1.

BRCA1-Regulated miRNAs

-miR-155 is a BRCA1-regulated oncogenic miRNA that targets PU.1 and p53INP1, involved in immune response and anti-apoptosis.

-miR-148 and miR-152 are tumor suppressors in endometrial cancer that are targeted by BRCA1.

-miR-205 targets ZEB1, ZEB2, and CK-epsilon, regulating EMT and invasion, and is targeted by BRCA1.

-miR-99b and miR-146a target TRAF2 and are involved in the NF-κB and MAPK pathways, regulated by BRCA1(39).

Correlation with p53

BRCA1 and p53 cooperatively regulate a subset of miRNAs, including miR-34a, miR-504, and miR-605, which target p53 and form a feedback loop.

-Mutant p53 can induce the expression of miR-155, which targets BRCA1, contributing to breast cancer progression (31).

These findings suggest a complex regulatory network involving BRCA1, BRCA2, p53, and miRNAs in breast cancer. Dysregulation of this network can contribute to tumor development and progression. Further research is needed to fully elucidate these interactions and their clinical implications (Table 6).

Table 6. included Key MicroRNAs in Breast Cancer (40)

miRNA	Role	Target Gens
miR-21	Oncogenic	PTEN, PDCD4, TPM1
miR-155	Oncogenic	FOXO3a, TP53INP1
miR-10b	Metastasis-promoting	HOXD10, RHOC
miR-373 and miR-520c	Metastasis-promoting	CD44
miR-205	Tumor suppressive	ZEB1/2, HER3
miR-335	Metastasis-suppressive	SOX4, TNC
miR-31	Metastasis-suppressive	RhoA, radixin, integrin-α5, RDX
miR-34a	Tumor suppressive	Notch1, Jagged1
miR-126 and miR-126*	Tumor suppressive	IRS-1, PIK3R2
miR-200 family	Metastasis-suppressive	ZEB1/2

Based on the provided search results, several studies have investigated the prognostic value of microRNAs (miRNAs) in breast cancer. Here are some key findings related to the prognosis risk ratio.

-A study found that higher baseline levels of total circulating miRNA (cf-miRNA) predicted patients at high risk of both death and relapse in breast cancer. In multivariate analysis, high cf-miRNA levels were an independent predictor of both overall survival (OS) and progression-free survival (PFS) (HR = 1.2, CI [1.01–1.41], P = 0.03) (41)

-Another study identified a three-miRNA signature (miR-127-5p, miR-340-5p, and miR-654- 3p) that could predict prognosis in breast cancer patients. Patients with high-risk scores based on this signature had a lower OS rate compared to those with low-risk scores. In multivariate analysis, the three-miRNA signature was an independent prognostic factor for poor prognosis (HR = 1.574, P = 0.014) (42).

-A systematic review highlighted that 110 aberrantly expressed miRNAs have been associated with prognosis in breast cancer. The authors also found six miRNA signatures that were useful for predicting the outcome of breast cancer (20).

-A study investigating the prognostic value of circulating miRNAs in triple-negative breast cancer (TNBC) revealed a four-miRNA signature (miR-18b, miR-103, miR-107, and miR-652) that could predict tumor relapse and overall survival (43).

These studies suggest that specific miRNAs and miRNA signatures have prognostic value in breast cancer, with higher risk scores or aberrant expression associated with poorer survival outcomes. However, the exact risk ratios vary among the studies due to differences in patient characteristics, sample types, and methodologies used. It's important to note that while these findings are promising, further validation in larger, independent cohorts is needed to establish the clinical utility of miRNAs as prognostic biomarkers in breast cancer. Additionally, standardization of miRNA detection methods and cut-off values for risk stratification will be crucial for translating these findings into clinical practice.

Regulation of miRNA Transcription and Synthesis

-The transcription and synthesis of miRNAs can be regulated by various factors, including transcription factors, epigenetic modifications, and RNA-binding proteins.

-Aberrant expression of miRNAs is frequently observed in human diseases, such as cancer, and can contribute to disease pathogenesis.

-Targeting the transcription and synthesis of miRNAs has emerged as a potential therapeutic strategy for diseases like cancer.

In summary, the majority of human miRNAs are transcribed by Pol II and undergo the canonical two-step nuclear and cytoplasmic processing to generate mature, functional miRNAs. However, alternative non-canonical pathways also exist that bypass one or more steps in this canonical biogenesis process. The transcription and synthesis of miRNAs are tightly regulated and can be dysregulated in human diseases, making them potential targets for therapeutic interventions (44).

The Future of MicroRNA in Cancer Prediction and Its Potential Impact on Healthcare

The future of microRNA in cancer prediction is promising, with ongoing research and technological advances paving the way for new discoveries and applications. As our understanding of the complex interplay between microRNAs and cancer deepens, we can expect the development of more accurate and reliable predictive models (45, 46). The potential impact of microRNA-based predictive methods on healthcare is vast. By enabling early detection and personalized treatment strategies, microRNAs have

the potential to reduce cancer-related morbidity and mortality. In addition, the non-invasive nature of MicroRNA testing makes it accessible to a wider population, ensuring that more people can benefit from early cancer detection and intervention (47, 48).

Conclusion

This review highlights the significance of microRNA in the revolution of cancer prediction, especially in the field of breast cancer. Its unique characteristics and its role in gene regulation make it an ideal biomarker for diagnosing and predicting the development and progression of breast cancer. By harnessing the power of microRNA, researchers and clinicians can create more accurate and personalized predictive models that have the potential to significantly improve patient outcomes and transform healthcare. The future of MicroRNA in cancer prediction is bright and its impact on healthcare is expected to be profound. As advances continue and challenges are overcome, microRNA-based predictive methods will undoubtedly play an important role in early diagnosis and effective management of cancer. By embracing this groundbreaking technology, we can unlock the full potential of MicroRNA and usher in a new era of precision medicine in the fight against cancer.

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Conflict of interest

The authors declare that no conflict of interest exists.

Authors' contributions

Conceptualization, Methodology, Supervision, Writing– Original Draft Preparation, Project Administration: FM, Validation, Resources, Visualization, Writing– Review & Editing: MK, Investigation: FM, MK

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