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ORIGINAL ARTICLE

MicroRNA 29 gene Expression and Progesterone Receptor Values in Iraqi Women with Breast Cancer

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ABSTRACT

Background: *Globally as well as in Iraq, Breast cancer (BC) is the most common malignant tumor among malignancies that affect women and one of the most deadly illnesses that affect women. MicroRNAs (miRNAs) are 18–25-nucleotides regulatory non coding short RNAs that post-transcriptionally control the expression of genes to perform a wide range of essential functions in various biological processes.* ***Objectives****: The study aimed to evaluate the miR-29a expression level and association with breast cancer as well as to find out the relationship between miR29 and Progesterone receptor.* ***Methodology:*** *There were 74 of blood samples (54 breast cancer patients and 20 healthy control group).RNA extracted from patients and controls to synthesize complementary DNA(cDNA).Gene expression of miR29a was carried out using the quantitative reverse transcription polymerase chain reaction (RT-qPCR).* ***Results:*** *The results revealed that miR-29a gene expression in patients with breast cancer was (1.276851852), while in healthy people, the 2^-(ΔΔCt) was equal to zero, with a standard error of (0.281) and a dispersion deviation of (2.069) in comparison with control group. It was noted that women with breast cancer had an increased concentration of progesterone receptors, where the average concentration for healthy people was 0.348.* ***Conclusion:*** *From these findings we concluded that miR29 can serve as biomarker, diagnostic or predictive tool upon diagnosing breast cancer in the medical laboratories and also for treatment development. There was a significant association between mir29a and PR levels in this study.*

INTRODUCTION

Breast cancer (BC) is the most prevalent cancer or tumor among malignancies that affect women and among the most deadly illnesses that affect women globally as well as in Iraq[1,2]. Breast cancer affects women due to hormonal changes or genetic mutations in DNA 3. In Iraq, It is the most prevalent cause of mortality for females with cancer and ranks first in the population 4-6.Breast cancer is a diverse disease in which both environmental and genetic factors are involved 7. Annually, Approximately 500,000 women do not survive the disease as well as die from breast cancer [8].

MicroRNAs (miRNAs) are 18–25-nucleotides regulatory and brief, non-coding RNAs which post-transcriptionally control the expression of genes to perform a wide range of essential functions in various biological processes[9-10]. MiRNAs control gene expression in a variety of ways, one of which involves their association with the 3'-end and, less frequently, the 5'-end of mRNA that is produced by target genes[11].

MicroRNAs (miRNAs) attach to 3′ UTR of their target messenger RNA (mRNA) to decrease production; they are essentially involved at the post-transcriptional level. The causes and mechanisms of cancer is connected with the disturbance of oncogenic or tumor-suppressive target gene expression caused by miRNA dysfunction[12]. Based on their severe dysregulation in a variety of cancer types, miRNA-29s are thought to exist as either oncogenic or tumor suppressors miRNAs[13]. Growing data suggests that the miR-29 family which includes (miR-29a, miR-29b-1, miR-29b-2, and miR-29c) as important biological process regulators. Furthermore, an array of illnesses are partly caused by their aberrant expression[14].

Noncoding RNAs, such as microRNAs (miRNAs), regulate target gene expression post-transcriptionally, which plays a part in the growth, metastasis, and breast cancer's carcinogenesis. miRNAs have the capacity to control gene targets in metastasis (metastamiRs), decrease tumor development (tumor suppressors, or miRsupps), and promote oncogenesis (oncomiRs)[13].

MicroRNA (miRNA) dysregulation plays a part in the carcinogenesis and progress in malignancies, particularly breast cancer (BC). Numerous investigations have revealed that miRNAs might act as oncogenes or tumor suppressors so that cancer development is one of the many effects of dysregulation of microRNA expression patterns[15-16].

However, microRNAs are significant stimulants that can serve as indicators of prognosis and diagnosis for different cancer types. Moreover, mutations in open-reading templates and microRNAs frequently result in cancer [17].

Cyclic hormonal stimulation of the tissues of breast has a major impact on breast carcinogenesis[18]. A key element of pathological assessment of BC is the assessment of hormone receptors expression. Hormone receptor testing is crucial because the results assist patient and physician in determining if hormonal therapy or other therapies are most likely to be effective in treating the cancer [19].

As an inducer of transcription, progesterone receptor (PR) plays essential roles in female reproduction as well as in the development of BC [20]. PR is a ligand-dependent transcription factor that belongs to the nuclear receptor family. Its primary function is to control target expression of a gene networks as a reaction to binding progesterone, the hormone that corresponds to it [21-22].

The aim of this study was to identify gene expression of mir 29 in BC patients in contrast to healthy groups and to find the connection between mir 29 expression level in association with progesterone receptor level additionally to find their effect as circulating biomarkers for a diagnosis in a medical environment.

METHODOLOGY

This research was carried out in National Hospital for Oncology and Hematology (NHOH) in Al-Najaf province and the Department of Biology / Faculty of Science in Laboratory of Molecular Biology – University of Kufa, in the time period starting from November 2022 to January 2024.

The study was carried out on 74 blood samples classified into patients with breast cancer 54 and healthy group 20. The tests were performed on the venous blood, which were collected from a healthy group and those with breast cancer. The total RNA was extracted from the samples by using Tryzol reagent (Ambion, USA) according to the manufacturer's guidelines.1ml blood was collected and placed in anticoagulant EDTA tubes then centrifuged at 5000 rpm for 5 minutes; the plasma was used freshly for the RNA extraction and PCR test. The microRNA 29a gene expression was estemated by the real time PCR in patients and healthy control. The quantitative reverse transcription polymerase chain reaction (RT-qPCR) was done using the primers mentioned by [23] in table (1). PR levels were measured by ELISA method[24].

Table 1: Primers sequences of *mir-29a*

Primer Sequence of *miR-29a*	
Forward primer	5' TCGTATCCAGTGCGTGTCGTGGAGTCGGC 3'
Reverse primer	5' AATTGCACTGGATACGACTAACCGA 3'

Statistical analysis:

The statistical analyses of all results were completed by the help of GraphPad Prism version 5 software statistical package by using t-test and Chi-square test (P value at level of the significance less than 0.05) to compare the values of results between the groups. Results values were expressed as mean ± SE, the number of patients[25].

RESULTS

The findings showed that a connection exists between the intensity of microRNA gene expression and BC, significant increase in gene expression was observed in all females with BC based on the value of delta-delta CT square, which represents number of the fold gene expression 2^-(ΔΔCt), where mean expression was equal to (1.276), while for the healthy group, 2^-(ΔΔCt) was equal to zero, with the standard error of 0.281 and the dispersion deviation of 2.069.As observed in the table (2) and shown in figure (1).

Table 2: The relationship of MicroRNA 29a gene expression between patients and healthy controls

Statistical analysis	**Progesterone Receptor**		**MiR-29a gene expression**	
	Healthy	**Patients**	**Healthy**	**Patients**
Average (Mean)	0.348581	0.578504	#N/A	**1.276851852**
median	0.1968	0.3898	#N/A	0.2
Standard division	0.430337	0.733877	#N/A	2.069182524
mode	0.0665	#N/A	#N/A	0.12
Standard error	0.058027	0.098956	#N/A	0.281580076

Table 3: Micro RNA expression and progesterone receptor

	MiR-29a gene expression	Progesterone Receptor
Average (Mean)	1.276851852	0.604325926
median	0.2	0.3898
Standard division	2.069182524	0.756621398
Standard error	0.281580076	0.102963131

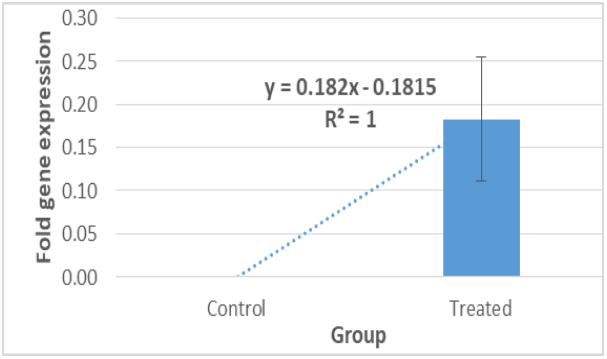

Fig. 1: The Fold gene expression of miRNA-29a.

The results also showed a positive correlation with the concentration of progesterone receptors between people suffering from BC and control people. The result was noted that females with BC had an increased concentration of progesterone receptors, where the average concentration for healthy people was 0.348, while for females with cancer, the average concentration was 0.578, with a standard error of 0.562 and 1.562 for healthy people and patients, respectively, with a dispersion deviation. It is 0.430 and 0.733 for healthy people and patients, respectively. (Table 4 and Figure 2).

Table 4: The progesterone receptor concentration in women with the breast cancer and healthy group

Statistical analysis	Progesterone Receptor	
	Healthy	Patients
Average (Mean)	0.348581	0.578504
median	0.1968	0.3898
Standard division	0.430337	0.733877
Standard error	0.058027	0.098956

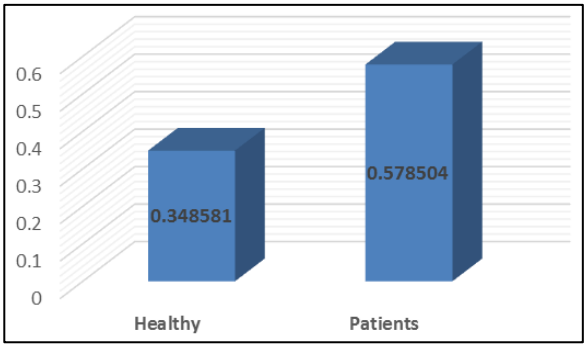

Fig. 2: The progesterone receptor concentration in the breast cancer patients and the healthy control.

There is a statistically significant relationship between gene concentration and the concentration of progesterone receptors. This can be inferred from t value and the associated p value. By indicating the F and p value, where the F value was 25.19 and with a significance of (0.000), which is smaller than 0.01, and the p value was 0.000 it can be concluded that the model is valid, and that there is a clear correlation between miRNA29a gene expression and of explanatory variables , concentration of progesterone receptors. In particular, between the gene expression of microRNA and concentration of the progesterone receptors, with an acceptable significance value of 0.000

The relationship between stages and genetic and hormonal variables:

The results showed that there's a relationship between the folding of the MicroRNA gene expression and early stages of BC, specifically the first stage IA,IB and the second stage, stage IIA,IIB a direct relationship with a significant percentage for the P factor, which was 0.000 (P-value = 0.000).While there's no relationship between the folding of the microRNA gene expression and the advanced stages of the BC , a lack of concentration was observed, as the mean was equal to 0.515 for the third stage (IIIA,IIIB) and 0.2662 for the fourth stage (IV). In contrast, it was 5.6175 for the first stage and 3.8675 for the second stage (Table 5).

This means that the microRNA gene expression increases at the beginning of the BC and its early stages as a means of defense or immunity to the disease, and this will be clarified later in the discussion.

Table 5: The relationship between the pathological stages of the breast cancer and the folding in microRNA 29a gene expression

Groups	*Count*	*Sum*	*Average*	*Variance*
stage IAB	12	44.94	5.6175	1.157593
stage IIAB	12	30.94	3.8675	1.418479
stage IIIAB	12	4.12	0.515	0.405229
stage IV	12	2.13	0.26625	0.029084

There is no significant correlation between the concentration of progesterone receptors and the stages of breast cancer, according to the statistical data as shown in table 6.

Table 6: Correlation between the pathological stages of breast cancer and the concentration of progesterone receptors

Groups	*Count*	*Sum*	*Average*	*Variance*
stage IAB	12	4.3609	0.545113	0.496601
stage IIAB	12	4.2565	0.532063	0.101488
stage IIIAB	12	5.0063	0.625788	0.455149
stage IV	12	3.5183	0.439788	0.016054

Expression of microRNA 29a concerning progesterone receptors and age groups

The statistical findings also demonstrated that, in accordance with the information in the table, there is no correlation between the patient's age and the level of gene expression, with the folding of microRNA 29a gene expression between age groups having a value of 0.721286 (P-value = 0.721286) according to results stated in the table 7.

Table 7: Age group relationships with microRNA 29a gene expression folding

Groups	*Count*	*Sum*	*Average*	*Variance*
0 - 29	10	2.46	0.351429	0.383581
30 - 39	10	4.47	0.638571	0.968581
40-49	10	2.99	0.427143	0.280357
50 - 59	10	8.16	1.165714	5.894795
+60	10	2.5	0.357143	0.397557

The findings showed that there was no significant correlation between age groups with concentration of progesterone receptors in blood of women with breast cancer, since value of correlation factor was 0. 0.652801 (P-value = 0. 0.652801), as there is no relationship to the amount of concentration of progesterone receptors along with the old age of the patient, according to what was stated in the table(8).

Table 8: Age group relationships with progesterone receptor concentrations

Groups	*Count*	*Sum*	*Average*	*Variance*
0 - 29	10	6.739	0.842375	1.262049
30 - 39	10	3.5063	0.438288	0.08447
40-49	10	3.2564	0.40705	0.040463
50 - 59	10	3.6983	0.462288	0.127493
+60	10	4.2872	0.5359	0.516622

The relationship between the side of the breast (right or left), progesterone receptors and the folding of MicroRNA-29a gene expression

The statistical results showed a significant relationship between the right side of the affected breast between the intensity of the microRNA gene expression 29a and the concentration of progesterone receptors where it was a significant relationship with a value of 0.0001263 P-value. Based on statistical analysis comparing the left breast to control samples, it was shown that there is no correlation between the concentration of progesterone receptors and the intensity of microRNA gene expression.

DISCUSSION

In the present study the gene expression of MiR29a was significantly increased in all BC patients according to the value of 2^-(ΔΔCt).

The MiRNA-29a's function in regulating the expression of genes and its connection to carcinogenesis might be the reason behind the rise in miRNA-29a expression. Patients with BC have been discovered to have dramatically changed levels of miRNA-29a in their blood, this indicates that miRNA-29a might be a new biomarker in BC[26].These results agree with a study which reported that levels of miRNA-29a gene expression in patients significantly

increased in cases compared with control (9.50±1.30 and 3.47± 0.70, respectively)$2^{\vee}$.The results we obtained are in agreement with previous studies[28-29] which showed that *miR-29a* were significantly higher in BC patients' serum (P<.05).

The recent findings weren't in line with a study found that *miR-29a* expression was notably decreased among individuals with BC when compared to the healthy individuals [30].

miRNA *miR-29a* was verified by Real-Time (RQ-PCR), demonstrating a notable decrease in *miR-29a* expression in the blood of patients as compared to that of healthy controls (p=0.001)[31].Aberrant microRNA expression contributes to breast cancer progression [32].

The study carried by Wu et al.[33], demonstrated that many kind of breast cancer cells have down-regulated levels of Mir-29a expression. These findings indicated that there is likely a connection between breast cancer and Mir-29a expression. According to the study of [33], an expression of Mir-29a was down-regulated in several forms of BC, and it was shown that Mir-29a is the most common isoform in its family in mammary cells.

Mohmoudian and his collagenous findings [34] showed the up regulation of miR-29a in the BC tumor in contrast to the matching surrounding tissues. They showed this miRNA was more highly expressed in HER-2 positive cells and tumor tissues, particularly in stage III of the TNM.

The family of miR-29 was down regulated in several tumors and it can suppress cancers for instance, breast, bladder, and pancreatic cancer [35-37]. Specifically, circulating miRNAs- which are present in cancer patient's blood and plasma in a sufficiently stable structure—are showing great promise as non-invasive indicators. Several investigations have examined the possible function of the circulating miRNAs in BC as therapeutic and prognostic indicators [38].

By focusing on various signaling pathways and messenger RNA transcripts, microRNAs (miRs) have been demonstrated to have an important role in the biology of human malignancies. In BC, miR-29 has mostly been described as a tumor suppressor, despite contradicting data and debatable involvement in a number of malignancies[39]. It has been demonstrated that miR-29 regulates several oncogenic pathways, making it a crucial miRNA in a variety of malignancies. While most research has provided comprehensive documentation of miR-29a as a suppressor of tumors, there is still some dispute around inconsistent claims of miR-29 in the capacity of an oncogene [26, 37].

Zhang *et al.*[40] found that At the G0/G1 phase, overexpression of miR-29a resulted in cell cycle arrest and miR-29a might aim to address the manifestation of cell division cycle[41] (CDC42), which is a tiny GTPase linked to the advancement of the cell cycle. Changes in microRNA (miRNA) are linked to metastasis and tumor development, and they are also utilized as biomarkers about the prognosis or diagnosis of breast cancer in addition to other diseases[41].

These results agree with the research of[42] that showed women with BC had considerably higher serum mean levels of the progesterone receptors than control individuals.

Based on results PR important biomarker to detect the BC incidence, and progesterone receptors are major targets in breast cancer, and as a result, the tumor's receptor status greatly influences for the duration of treatment.

CONCLUSION

The present study showed that an expression of *mir-29a* was significantly related to the BC incidence also there was a strong correlation between mir29 and serum levels of PR in comparision between patients and controls .Also a statistically noteworthy correlation between mir29 and both age , stage and side of BC in the patients was reported.According to our results ,mir 29 can be utilized as possible indicators in medical laboratories to detect this cancer .Further research is required to confirm the current results.

Ethical Approval Declaration

The procedures followed in this study were in accordance with the regulations of the relevant clinical research ethics committee In addition, each participant provided written consent following a concise overview of the project.

Declarations:

Consent for publication: Not applicable

Availability of data and material: Data are available upon request.

Competing interests: The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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