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Evaluation of SIRT1-Regulating miRNAs in Breast Cancer: miR-9, miR-34a, and miR-132 Expression Analysis

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ABSTRACT

Purpose: Breast cancer is one of the most common malignancy for women and one of the most common causes of cancer related deaths for women. Genetic factors and family history play major roles in its etiology. For a possible genetic treatment genetic pathway should be illuminated.

Materials and Methods: The miRNeasy Mini Kit was used to isolate total RNA from tissues and normal breast tissues in patients with breast cancer who underwent mastectomy for treatment. Expression levels of miRNAs were measured and normalized with U6 gene.

Results: After measurement of expression levels, normalizing with U6 gene and statistical analysis, we found that there was no statistically significant difference between breast cancer tissues and normal breast tissues.

Conclusion: Limited number of studies reported that the levels of all three micro RNAs were found to be lower in breast cancer tissues than in normal breast tissue. In this study, no statistically significant difference was found between normal breast tissue and breast cancer tissues in terms of levels of these micro RNAs for all three micro RNAs.

Since there is conflicting and incomplete information about the SIRT1 enzyme in the literature, it is not unexpected that the results of our study are incompatible with the literature. Further studies are needed to clearly elucidate the mechanisms of SIRT1 and its regulating micro-RNAs.

In the studies to be done, the determination of the microRNA levels simultaneously with SIRT1's own expression levels can be enlightening on this issue.

Keywords: Breast Neoplasms, Sirtuin 1, MicroRNAs, MicroRNA-9, MicroRNA-34a, MicroRNA-132

ÖZET

Amaç: Meme kanseri kadınlarda en sık görülen malignitelerden biridir ve kadınlarda kansere bağlı ölümlerin en sık nedenlerinden biridir. Etiyolojisinde genetik faktörler ve aile öyküsü önemli rol oynamaktadır. Olası bir genetik tedavi için genetik yolun aydınlatılması gerekmektedir.

Gereç ve Yöntem: MiRNeasy Mini Kit, mastektomi yapılan meme kanseri tanılı hastaların kanserli dokularından ve normal meme dokularından total RNA'nın izole edilmesi için kullanıldı. MiRNA'ların ekspresyon seviyeleri ölçüldü ve U6 geni ile normalize edildi.

Bulgular: Ekspresyon düzeylerinin ölçümü, U6 geni ile normalizasyon ve istatistiksel analiz sonrasında meme kanseri dokuları ile normal meme dokuları arasında istatistiksel olarak anlamlı bir fark olmadığı tespit edildi.

Tartışma: Sınırlı sayıda çalışma, her üç miRNA'nın da meme kanseri dokularında normal meme dokusuna göre daha düşük düzeyde bulunduğunu bildirmiştir. Bu çalışmada normal meme dokusu ile meme kanseri dokuları arasında her üç mikro RNA için de bu mikro RNA'ların düzeyleri açısından istatistiksel olarak anlamlı bir fark bulunamadı.

Literatürde SIRT1 enzimi ile ilgili çelişkili ve eksik bilgilerin olması nedeni ile çalışmamızın sonuçlarının literatürle uyumsuz olması beklenmedik değildir. SIRT1'in mekanizmalarını ve düzenleyici micro RNA'larını net bir şekilde aydınlatmak için daha ileri çalışmalara ihtiyaç vardır.

Yapılacak çalışmalarda SIRT1'in kendi ekspresyon seviyeleri ile eş zamanlı olarak microRNA seviyelerinin belirlenmesi bu konuda aydınlatıcı olabilir.

Anahtar Kelimeler: Meme Neoplazmları, Sirtuin 1, MicroRNA, MicroRNA-9, MicroRNA-34a, MicroRNA-132

Breast cancer is one of the most common malignancy for women and one of the most common causes of cancer related deaths for women. Every year more than 1 million new cases are diagnosed with breast cancer in the world, and the second most common cause of cancer-related deaths in women is breast cancer (1).

Although there are new treatment approaches, it is still an important health problem because of its increasing incidence. Breast cancer is a multifactorial disease that many factors are playing roles in its etiology. Genetic factors and family history play major roles in its etiology. For a possible genetic treatment genetic pathway should be illuminated.

One of the worthwhile processes in the treatment of breast cancer is to reveal the effects of SIRT1, a member of the class III HDAC (histone deacetylase family), and the effects of miRNAs (micro-RNAs) involved in the regulation of this enzyme.

miRNAs are approximately 23 nt RNAs that do not code, and they show their effects by suppressing the translation or rendering target mRNAs unstable. miRNAs play an active role in many important processes such as proliferation, differentiation, apoptosis.

SIRT1 is known to play a key role in many physiological processes such as genome stability, metabolism, cell survival, and neurogenesis.

Deacetylase function of SIRT1 is thought to be associated with prolongation of survival in mammals. Because of this property, this protein is thought to act as a tumor promoter in the development of many cancers.

SIRT1 has been shown to be significantly higher in human prostate cancer (2), acute myeloid leukemia (3) and primary colon cancer (4). It is claimed that SIRT1 is high in such cancer tissues and it is the tumor promoter (5).

In another study, SIRT1 has been shown to be found in lower rates in some cancer tissues such as glioblastoma, gallbladder cancer, prostate cancer and ovarian cancer compared to normal tissues (6). Again in this study, in the analysis of 44 breast cancer cases lower SIRT1 expression was found in cancerous tissues compared to normal tissues (6).

A comparison study of tumor and normal tissues of breast cancer patients between 2007 and 2008, has shown that there was a strong correlation between SIRT1 and Ki67 (Antigen Kiel 67), and at the inhibition of SIRT1 by sirtinol, there was a dramatic decline at the levels of life extruder bcl-2 (B-cell lymphoma 2) proteins in cancer tissue. These results make us to think that inhibition of SIRT1 can be used as a strategy in the chemotherapy of breast cancer. The results of RT-PCR (reverse transcription polymerase chain reaction) indicate that SIRT1 miRNA levels were found to be higher in tumor tissues than normal tissues. (92.59%, n=27) (7).

Many studies have investigated the relationship of various micro RNAs with SIRT1. So far, more than sixteen micro-RNAs have been thought to be associated with breast cancer, and studies have been conducted to support this. These miRNAs are miRNA-449a, miRNA-449, miRNA-22, miRNA-200a, miRNA-34a, miRNA-143/145, miRNA-217, miRNA-195, miRNA-199a, miRNA-132, miRNA-181c miRNA-9, miRNA-93, miRNA-181a/b, miRNA-204, miRNA-199b, miRNA-15a, miRNA-100 (8).

There were very few studies on the levels of miRNA-9, miRNA-34a and miRNA132 in breast cancer tissues, that's why we decided to investigate a possible relation between SIRT1 (Silent mating-type information regulation 2 homologue 1) and this miRNAs.

The aim of this study was to investigate the levels of SIRT1-related miRNAs in cancer tissues and normal breast tissues in patients with breast cancer who underwent mastectomy for treatment.

Material and Methods

The miRNeasy Mini Kit (Qiagen GmbH, Hilden, Germany) was used to isolate total RNA (containing miRNA) from fresh tissue. Then, the cDNA (Complementary DNA) synthesis from miRNA was performed using the Qiagen miScript Reverse Transcription (RT) Kit II (Hilden, Germany).

The amounts of cDNA were adjusted to 50 ng / µl and made ready for use for qRT-PCR. cDNAs were stored at -80 ° C to extend the lifetime of them. The reaction components for qRT-PCR were then prepared using the Qiagen miScript SYBR Green PCR kit. The reaction components were prepared on ice and dispensed with cDNAs into appropriate tubes and loaded onto the qRT-PCR Rotor-Gene Q (Qiagen) instrument and the reaction was carried out.

Results

A total of 66 patients who underwent surgery for breast cancer in Gaziantep University Şahinbey Training and Research Hospital between 2012-2016 were included in the study. (Table 1 and Table 2) During the operation, samples from cancer tissues and normal breast tissues of these patients were taken and stored in nitrogen tanks and recorded. A total of 132 tissue samples were used in the study. Statistical analyses were performed using SPSS for Windows 26.0.

Table 1. Statistical information about patients

	Female	**Male**	
Gender	66	-	
	Female	Male	All patients
Average age	50.8	-	50.8
	Invasive ductal carcinoma	Invasive lobular carcinoma	Other
Histopathological diagnosis	56(84.8%)	7(10.6%)	3(4.5%)
	Estrogen (+)	Progesterone (+)	c-erb b2 (+)
Receptor	50 (75.7%)	49 (74.2%)	24 (36.3%)
	Stage-1	Stage-2	Stage-3
Disease stage	5 (7.5%)	31 (46.9)	30 (45.4)

Table 2. Patients List (ER: estrogen receptor, PR: progesterone receptor, N: Negative, P: Positive)						
	Age	**Histopathological Diagnosis**	**Stage**	**ER**	**PR**	**C-ERB-B2**
Patient-1	63	Metaplastic carcinoma	3	N	N	N
Patient-2	57	Invasive ductal carcinoma	1	P	N	N
Patient-3	36	Invasive ductal carcinoma	2A	P	N	N
Patient-4	44	Invasive ductal carcinoma	2A	P	N	N
Patient-5	44	Invasive ductal carcinoma	2A	P	N	N
Patient-6	44	Invasive ductal carcinoma	2A	P	N	N
Patient-7	48	Invasive ductal carcinoma	2	N	P	N
Patient-8	50	Invasive ductal carcinoma	2B	P	P	N
Patient-9	62	Invasive ductal carcinoma	2	P	P	N
Patient-10	57	Invasive ductal carcinoma	2A	P	P	N
Patient-11	62	Invasive ductal carcinoma	2	P	P	N
Patient-12	62	Invasive ductal carcinoma	2	P	P	N
Patient-13	55	Invasive ductal carcinoma	3A	P	P	N
Patient-14	66	Invasive ductal carcinoma	2B	P	P	N
Patient-15	35	Invasive ductal carcinoma	2B	P	P	N
Patient-16	47	Invasive ductal carcinoma	2	P	P	N
Patient-17	59	Invasive ductal carcinoma	1	P	P	N
Patient-18	44	Invasive ductal carcinoma	2	P	P	N
Patient-19	42	Invasive ductal carcinoma	3A	P	P	N
Patient-20	42	Invasive ductal carcinoma	3A	P	P	N
Patient-21	65	Invasive ductal carcinoma	2B	P	P	N
Patient-22	59	Invasive ductal carcinoma	3	P	P	N
Patient-23	49	Invasive ductal carcinoma	2B	P	P	N
Patient-24	57	Invasive ductal carcinoma	3	P	P	N
Patient-25	42	Invasive ductal carcinoma	2	P	P	N
Patient-26	44	Invasive ductal carcinoma	3B	P	P	N
Patient-27	44	Invasive ductal carcinoma	3B	P	P	N
Patient-28	44	Invasive ductal carcinoma	3B	P	P	N
Patient-29	44	Invasive ductal carcinoma	2	P	P	N
Patient-30	44	Invasive ductal carcinoma	2	P	P	N
Patient-31	38	Invasive ductal carcinoma	3	P	P	N
Patient-32	42	Invasive ductal carcinoma	3	P	P	N
Patient-33	42	Mixed (IDC + ILC)	2	P	P	N
Patient-34	69	Invasive lobular carcinoma	2	P	P	N
Patient-35	70	Invasive lobular carcinoma	2B	P	P	N
Patient-36	67	Invasive lobular carcinoma	3	P	P	N
Patient-37	56	Invasive lobular carcinoma	4	P	P	N
Patient-38	56	Invasive lobular carcinoma	4	P	P	N
Patient-39	42	Invasive lobular carcinoma	3	P	P	N
Patient-40	61	Mixed (IDC + ILC)	3	P	P	N
Patient-41	78	Invasive ductal carcinoma	1	P	P	N
Patient-42	44	Invasive ductal carcinoma	3C	N	N	P
Patient-43	44	Invasive ductal carcinoma	3C	N	N	P
Patient-44	38	Invasive ductal carcinoma	3B	N	N	P
Patient-45	48	Invasive ductal carcinoma	3	N	N	P
Patient-46	49	Invasive ductal carcinoma	3B	N	N	P
Patient-47	48	Invasive ductal carcinoma	3	N	N	P
Patient-48	51	Invasive ductal carcinoma	2A	N	N	P
Patient-49	48	Invasive ductal carcinoma	3	N	N	P
Patient-50	47	Invasive ductal carcinoma	2A	P	N	P
Patient-51	35	Invasive ductal carcinoma	3	P	N	P
Patient-52	52	Invasive ductal carcinoma	4	N	P	P
Patient-53	45	Invasive ductal carcinoma	2	N	P	P
Patient-54	45	Invasive ductal carcinoma	2	N	P	P
Patient-55	60	Invasive ductal carcinoma	3	N	P	P
Patient-56	60	Invasive ductal carcinoma	3	N	P	P
Patient-57	84	Invasive ductal carcinoma	3	N	P	P
Patient-58	45	Invasive ductal carcinoma	2	P	P	P
Patient-59	44	Invasive ductal carcinoma	2B	P	P	P
Patient-60	57	Invasive ductal carcinoma	3A	P	P	P
Patient-61	52	Invasive ductal carcinoma	1	P	P	P
Patient-62	52	Invasive ductal carcinoma	1	P	P	P
Patient-63	62	Invasive ductal carcinoma	2	P	P	P
Patient-64	34	Invasive ductal carcinoma	2b	P	P	P
Patient-65	34	Invasive ductal carcinoma	2b	P	P	P
Patient-66	46	Invasive lobular carcinoma	3C	P	P	P

Findings for miRNA-132

For miRNA-132, level analysis was performed in 132 tissue samples from 66 patients. In 33 of 66 patients, miRNA-132 levels in tumor tissue decreased compared to normal tissue, remained unchanged in 11 patients and increased in 22 patients. The detected levels were normalized by proportioning to U6 (housekeeping gene). In normal and tumor tissue groups, miRNA-132 expression levels were compared with U6 expression level by 2-ΔCt method and the fold change value was obtained for these genes. After normalization for both groups, the data were analyzed by Student's T Test. In the analysis, no statistically significant difference was found between breast cancer tissues and normal breast tissues in terms of miRNA-132 levels in 66 patients with breast cancer. (P=0.42) (Table 3 and Fig. 1)

Table 3. Comparison of miRNA-132 levels (normalized) in tumor and normal tissues.

T-TEST RESULTS OF NORMALIZED miRNA-132 LEVELS		
	Normal Tissue	*Tumor Tissue*
Average	0.498871773	0.568772895
Variance	2.310752339	6.014650874
Observation	66	66
Projected Average Difference	0	
Df	109	
t Stat	-0.196812861	
P(T<=t) one-tailed	0.422170247	

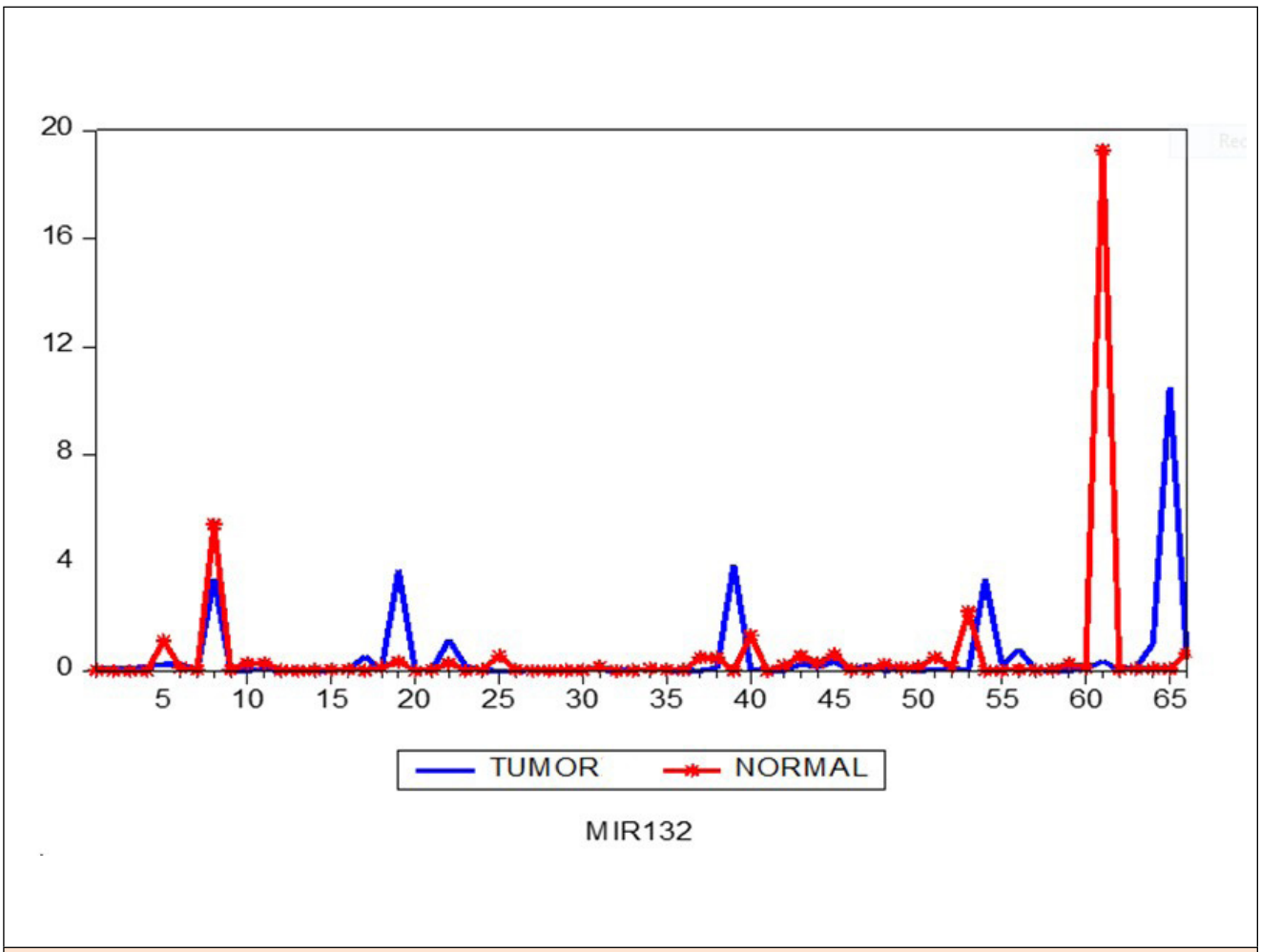

Figure 1: miRNA-132 levels of normal and tumor tissues for each patient.

Findings for miRNA-34A

For miRNA-34a, level analysis was performed on 132 tissue samples from 66 patients. In 20 of these 66 patients, miRNA-34a levels in tumor tissue decreased compared to normal tissue, remained unchanged in 16 patients and increased in 30 patients. The determined levels were normalized by proportioning to U6 level. In normal and tumor tissue groups, miRNA-34a expression levels were compared with U6 expression level by 2-ΔCt method and a fold change value was obtained for these genes. After normalization for both groups, the data were analyzed by Student's T Test. In the analysis, no statistically significant difference was found between breast cancer tissues and normal breast tissues in terms of miRNA-34a levels in 66 patients with breast cancer. (P=0.39) (Table 4 and Fig. 2)

Table 4. Comparison of miRNA-34a levels (normalized) in tumor and normal tissues.

T-TEST RESULTS OF NORMALIZED miRNA-34a LEVELS		
	Normal Tissue	*Tumor Tissue*
Average	1.564416519	1.35568886
Variance	16.26777161	28.13214371
Observation	66	66
Projected Average Difference	0	
Df	121	
t Stat	0.254484243	
P(T<=t) one-tailed	0.399776731	

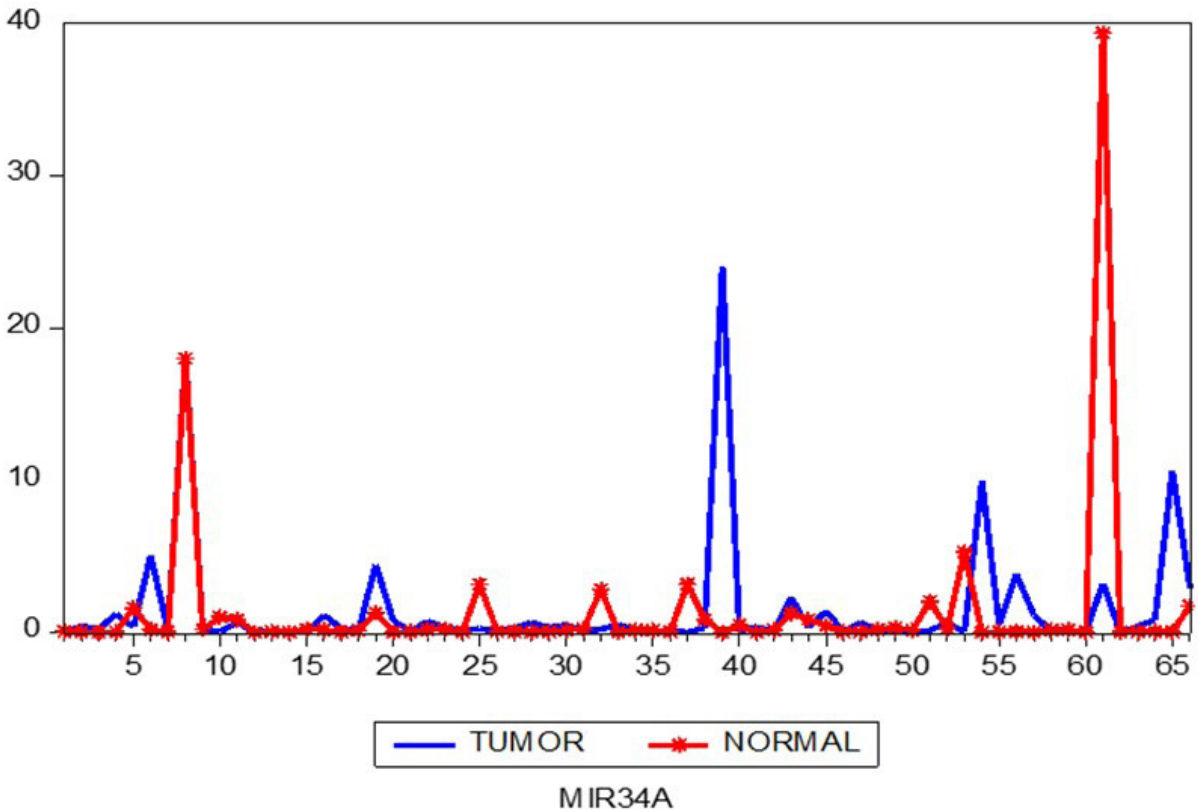

Figure 2: miRNA-34a levels of normal and tumor tissues for each patient.

Findings for miRNA-9

Level analysis was performed in 94 tissue samples taken from 47 patients for miRNA-9. (19 patients could not be analyzed for technical reasons) In 24 of 47 patients, miRNA-9 levels in tumor tissue decreased compared to normal tissue, remained unchanged in 4 patients and increased in 19 patients. The determined levels were normalized by proportioning to U6 level. By using the 2-ΔCt method, miRNA-9 expression levels in normal and tumor tissue groups were compared with U6 expression level and the relative coefficient value was obtained for these genes. After normalization for both groups, the data were analyzed by Student's T Test. In the analysis, 47 patients with breast cancer had no statistically significant difference between breast cancer tissues and normal breast tissues in terms of miRNA-9 levels. (P=0.17) (Table 5 and Fig. 3)

Table 5. Comparison of miRNA-9 levels (normalized) in tumor and normal tissues.

T-TEST RESULTS OF NORMALIZED miRNA-9 LEVELS		
	Normal Tissue	*Tumor Tissue*
Average	0.150194972	0.036329229
Variance	0.668264404	0.007031406
Observation	47	47
Projected Average Difference	0	
Df	47	
t Stat	0.949937406	
P(T<=t) one-tailed	0.173501725	

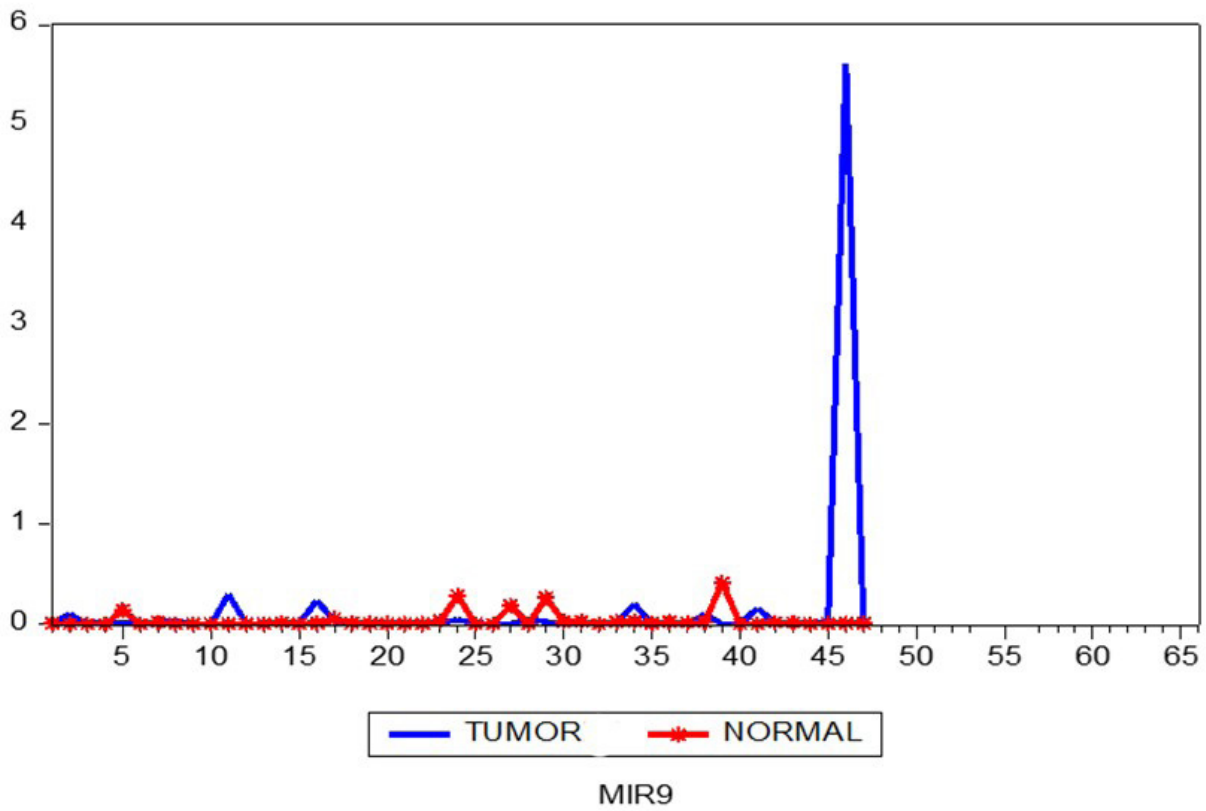

Figure 3: miRNA-9 levels of normal and tumor tissues for each patient.

Discussion

Nowadays, it is thought that genetic studies may lead a new way in the treatment of breast cancer which especially in female patients is a very important health problem and still causing serious mortality. One of the enzymes frequently investigated for this purpose is SIRT1, one of the members of the family of sutures. Relationships between increased or decreased levels of SIRT1 in tissue and many types of cancer have been established and a limited number of therapeutic interventions have been tried.

Studies to ensure regulation of SIRT1 have shown that more than 16 miRNAs are involved in SIRT1 regulation so far. These miRNAs were; miRNA-449a, miRNA-449, miRNA-22, miRNA-200a, miRNA-34a, miRNA-143/145, miRNA-217, miRNA-195, miRNA-199a, miRNA-132, miRNA-181c, miRNA -9, miRNA-93, miRNA-181a / b, miRNA-204, miRNA-199b, miRNA-15a, miRNA-100. Of these, miRNA-34a was the most studied (8). (Figure 4)

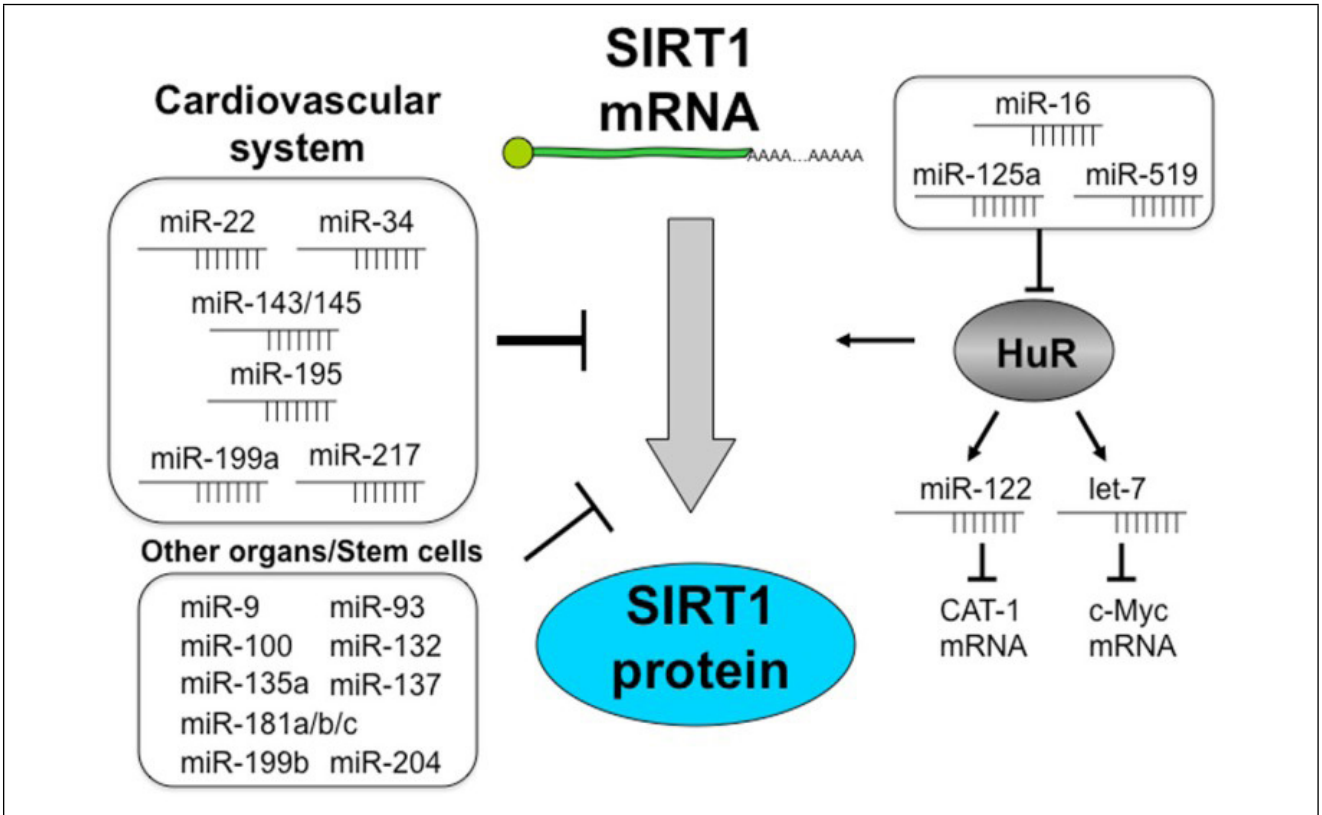

Figure 4: SIRT1 regulation with miRNAs. It is shown that miRNAs regulate SIRT1 expression and functions directly and via HuR. miRNA-22, miRNA-34, miRNA-143/145, miRNA-195, miRNA-199a and miRNA-217 are found in vascular tissue and control SIRT1 protein. There are more than 16 miRNAs which regulate SIRT1 [12].

ABBREVIATIONS:

APC:	Adenomatous polyposis coli
BRCA-1:	Breast cancer gene 1
cDNA:	Complementary DNA
ER:	Estrogen receptor
HDAC:	Histone deacetylase family
IDC:	Invasive ductal carcinoma
ILC:	Invasive lobular carcinoma
miRNA:	Micro RNA
PR:	Progesterone receptor
RNA:	Ribonucleic Acid
RT-PCR:	Reverse transcription polymerase chain reaction
SIRT1:	Silent mating-type information regulation 2 homologue 1
qRT-PCR:	Quantitative real time reverse transcriptase
Ki-67:	Antigen Kiel 67

Although there are many studies on micro RNAs involved in the regulation of SIRT1 in the literature, the diversity of micro RNAs and their presence in many different tissues and their important roles in these tissues prevented them from focusing on a specific area. Therefore, there were very few studies on the levels of miRNA-9, miRNA-34a and miRNA132 micro-RNAs analyzed in breast cancer tissues in this study.

In a study conducted in 2008, it was shown that inhibition of SIRT1 with a specific inhibitor leads to hyperceretylation of p53 and increased p53-related transcription (10). Firestein et al. showed that the overexpression of SIRT1 in APC + (Adenomatous polyposis coli) rats resulted in a decrease but not an increase in colon cancer formation (11).

Wang et al showed lower levels of SIRT1 of BRCA-1-related breast cancer (Breast cancer gene 1) compared to BRCA-1 unrelated breast cancers in their analysis (12). They further stated that BRCA1 binds to the SIRT1 promoter and regulates it positively at both protein and mRNA levels and that BRCA1 defect may cause cancer transformation in BRCA1 mutant cells with decreasing SIRT1 levels.

In this study, three microRNAs thought to be associated with SIRT1 were studied: miRNA-132, miRNA-34a and miRNA-9. miRNA-34a, one of the miRNAs whose breast cancer relationship was questioned, has been shown to play a role in liver fat metabolism, b-cell exocytosis and cell apoptosis. miRNA-132 is involved in the production of stress-induced chemokine while miRNA-9 has been shown to play a role in insulin secretion (13).

miRNA34a has been shown to be low levels in cancer tissue of many organs (14).In another study, it was shown that the expression of this micro RNA in endothelial cells increased considerably and decreased its level by targeting SIRT (15). Decreased levels of this miRNA have also been shown in an analysis of prostate cancer tissues (16). In a study conducted in patients with hepatocellular cancer, miRNA-34a was shown to be inhibited by FXR receptors (Farnesoid X receptor) and as a result positive regulation of SIRT1 could be achieved. Only one study showed that miRNA-34a was found to be lower than normal in breast cancer tissues and it was suggested that correcting this may increase the response to radiotherapy in breast cancer (17).

Although miRNA-9 is detected at low levels in many cancer tissues, it is not yet possible to classify it as a tumor suppressor or a carcinogenic miRNA. It was found to be increased in brain tumors (18) but low in breast cancer with metastasis, hepatocellular cancer, gastric carcinoma, ovarian cancer and malignant melanoma (19). On the other hand, epigenetic inactivation of miRNA has also been found in breast cancer, colorectal cancer and renal cell carcinoma (20). In a specific study on the relationship between miRNA-9 and breast cancer, lower miRNA-9 levels were also found in tumor tissues compared to normal tissues (21).

Increased levels of miRNA-132 have been shown in pancreatic cancer. In breast cancer investigations, this micro-RNA was found to be low in in-situ breast cancer tissues and was interpreted as behaving as a tumor suppressor (22). Similarly, in another study, miRNA-132 level was found to be decreased in breast cancer tissues (23).

Conclusion

Limited number of studies reported that the levels of all three micro RNAs were found to be lower in breast cancer tissues than in normal breast tissue. In this study, no statistically significant difference was found between normal breast tissue and breast cancer tissues in terms of levels of these micro RNAs for all three micro RNAs.

Since there is conflicting and incomplete information about the SIRT1 enzyme in the literature, it is not unexpected that the results of our study are incompatible with the literature. Further studies are needed to clearly elucidate the mechanisms of SIRT1 and its regulating micro-RNAs.

In the studies to be done, the determination of the microRNA levels simultaneously with SIRT1's own expression levels can be enlightening on this issue. The fact that these micro RNAs are at normal levels despite the low levels of SIRT1, or that the levels of these micro RNAs remain normal despite the high levels of SIRT1 may provide more illuminating data for the relationship between SIRT1 and these micro RNAs.

Declarations

Funding

Not applicable

Conflicts of interest/Competing interests

All authors declare that they have no conflicts of interest.

Ethics approval

Ethics committee approval was received for this study from the ethics committee of Gaziantep University (18.05.2015/157). Informed consent for the use of their data/samples was obtained from all participants.

Availability of data and material

All of the data is available if necessary.

Authors' contributions

M. Elçi, A. Aytekin, N. Aksoy, G. Maralcan

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This study is Muhsin Elçi's thesis and is stored with 435714 number in Higher Education Council archive.

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