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# *Relationship Between Two Key Non-Coding RNAS in Breast Cancer: HOTAIR and miR-331-3p*

***Tajik Arefeh[1]; Talesh Sasani Soheila[2]*; Fakour Fereshteh[2]; Mahjoubi Elahe[1]***

*[1]M.Sc in Genetics, Department of Biology, Faculty of Sciences, University of Guilan, Iran.*

*[2]Associate Professor of Obstetrics and Gynecology, Medicine School, Guilan University of Medical Science, Iran.*

## Abstract

**Background:** Non-coding RNAs are implicated in several tumor types, such as oncogenes or tumor suppressors, via target gene expression regulation. Breast Cancer (BC) is most prevalent among females in the world. Although, some studies revealed expression changes of miR-331-3p and HOTAIR genes in BC, to our knowledge, this is the first report about the relationship between the two genes in breast cancer.

**Materials and methods:** In this case-control research, 30 BC tumoral (case) and 30 adjacent normal tissue (control) samples were obtained to investigate miR-331-3p and HOTAIR expression. Total RNA was extracted using Tirol reagent, and cDNA synthesis was carried out. Relative expression of the genes was evaluated using quantitative real-time polymerase chain reaction (QRT-PCR).

**Results and discussion:** Statistical analysis of the data revealed significantly increased expression levels of both genes. So, miR-331-3p and HOTAIR high expression was nearly three (2.8±0.34 vs 1.05±0.21) and two times (1.97±0.36 vs 1.04±0.24), respectively, in the BC samples compared to the normal specimens ($p<0.05$). Based on the results, high expression of both genes in tumoral specimens compared to normal samples was obtained. Considering HOTAIR activity as a miR-331-3p sponge leading to a reduction of the miRNA amount, our study demonstrated different results in BC. Several factors affect miRNA-target interactions, such as compensatory transcriptional activation and intracellular compartment-specific expression patterns. So, it may be said that miR-331-3p acts as a tumor suppressor, and its elevated amount is probably in contrast to HOTAIR's function as an oncogene. More studies on a large number of participants are necessary in the future.

**Keywords:** Breast cancer; Gene expression; Lncrna; Microrna.

## Introduction

Breast Cancer (BC) is the most common cancer type among women; although the cancer is not limited to females, it is rarely seen in men (only 0.5-1% of breast cancers are found in men) [1]. In Iran, based on the GLOBALCAN 2020 report, breast cancer was recognized as the most abundant type of cancer with a rate of 12.9% among all cancers, and its prevalence is increasing intensively [2]. Diverse risk factors, such as inheritance, age, gender, lifestyle, etc., affecting BC susceptibility, initiation, and promotion are categorized into three main groups: genetic, epigenetic, and environmental [3]. Inheritance is a very important factor in the occurrence of the disease, and many genes are involved in breast cancer appearance, including the genes that affect the cell cycle. In this case, two groups of genes have been identified, and their dysregulation can lead to cancer occurrence. Oncogenes are a deregulated form of proto-oncogenes, a class of genes whose normal function is essential for cell proliferation. Their overexpression leads to cancerous phenotypes, such as c-MYC, RAS, and HER2, having a decisive role in breast cancer.

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**Correspondance:** *Talesh Sasani Soheila, Associate Professor, Department of Biology, University of Guilan, Iran.*

*Tel: +989111397401; Email: sasani@guilan.ac.ir*

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On the other hand, there are tumor-suppressor genes preventing uncontrolled cell division and some cancerous actions, so the downregulation of the genes is an important cause of BC [4]. For example, p53, p21, p27 [5], and the Inhibitor of the Growth 5 (ING5) gene, a target gene of miR-331-3p [6], and many other genes, so that 64 candidate genes are introduced as tumor suppressors [7].

Non-coding RNAs are involved in several gene expression regulations at the post-transcriptional level. The molecules include different types of RNA, such as long non-coding RNAs (LncRNAs) and microRNAs (MIRS). MicroRNAs are non-coding small RNAs, 18-22 nucleotides in length, regulating the expression of several genes, over 60% of encoding genes [8], via binding to the 3′-untranslated region (3′- UTR) of the target mRNAs, causing degradation or inhibition of their translation [9]. These small RNAs have an important role in cancer appearance and progression as oncogenic factors (ONCOMIRS) or as Tumor Suppressors (TS-MIRS), although some of them have dual functions based on the cell context [7,10]. It has been revealed that microRNAs are involved in different types of cancer. There are increasing studies on the important role of microRNAs in BC initiation, progression, and metastasis. The studies demonstrated that miRNAs may be a hopeful biomarker in cancer. Due to the abundance of MIRS and their stability in different body fluids such as blood, using these small RNAs as a biomarker is a non-invasive and easy procedure for early diagnosis, prevention of disease progression, personalized and purposeful treatment of breast cancer [11,12].

Moreover, LNC-RNAs are some non-coding RNAs with a length of more than two hundred nucleotides that are involved in cancer pathogenesis by regulating the different effective molecules in the disease initiation and progression including micro-RNAs [13]. HOTAIR, as an oncogenic lncRNA, with more than 2 kb in length, is known as one of the most important regulators of chromatin status and different genes expression [14,15]. Extensive research demonstrated that an interaction between HOTAIR and its target molecules, including miRNAs, plays an effective role in cancer onset and progression [16-18]. High expression of HOTAIR is detected in original tumors and metastatic breast cancer. It has been reported that HOTAIR binds to miR-331-3p, affecting its function [19]. Furthermore, a correlation between HOTAIR and miR-331 has been indicated in gastric cancer [6]. Considering the increasing frequency of BC worldwide, and due to the specific function of non-coding RNAs in the prevalence of breast cancer, they are attractive molecules as diagnostic and therapeutic targets. So, we studied the association of two key ncRNAs (HOTAIR and miR-331-3p) gene expression changes in cancerous and healthy breast tissue samples.

## Materials and methods

We conducted a case-control study to evaluate the relationship between miR-331 and HOTAIR expression levels in breast cancer patients. The research included 30 women suffering from the disease. Breast tissue samples were obtained from tumors and their normal margins as case and control groups, respectively. The samples were collected from Ghanem Hospital (Rasht, Iran) between November 2020 and March 2021. The participants' age range was between 30 and 60 years, and the patients who received chemotherapy or radiotherapy prior to entrance to our study were excluded. Also, the patients with a history of malignancy and other diseases that require specific medications, such as diabetes and cardiovascular diseases, were rejected in this study. Pathobiological features of all enrolled subjects were obtained from their medical records. The characteristics included age, breastfeeding, BMI, menarche age, menopausal status, oral contraceptive pills history, breast cancer family history, tumor site and size, staging, Lymph Node (LN) status, Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) status. The contributors were informed about the research aims by written consent according to the protocol introduced by the ethical standards of the institutional and/or national research committee and in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Total RNA isolation and cDNA synthesis:** The breast tissue samples were collected in RNase-free EDTA-coated tubes and transported by a liquid nitrogen flask to the genetics laboratory, Faculty of Sciences, University of Guilin, to be stored at -70°C until use. To extract total RNA, the tissue samples were powdered using liquid nitrogen, and the Tirol reagent (Invitrogen, California, USA) was used according to the instructions of the company. Genomic DNA was eliminated from the extracted RNA using a DNase kit (Thermo Fisher Scientific, Massachusetts, USA) according to the manufacturer's recommendation. Quantitative evaluation of the RNA was carried out via a Nanodrop spectrophotometer (Thermo Fisher Scientific, Massachusetts, USA), and estimation of the optical density at 260 /280 nm was carried out. Also, the RNA quality was assessed by agarose gel (2%) electrophoresis to observe three bands (28s, 18s, and 5.8s) related to ribosomal RNAs, indicating a good extraction. Because microRNAs do not have a Poly A tail, we first conducted polyadenylation of them by using E. coli poly(A) polymerase and a Poly(A) tailing kit (New England Biolabs, Mass, USA), according to the manufacturer's recommendation. Complementary DNA synthesis was done by a cDNA synthesis kit (Thermo Fisher Science, Massachusetts, USA) according to the manufacturer's protocol. Although we used anchored oligo dT (5'GCGTCGACTAGTACAACTCAAGGTTCTTCCAGTCACGACG (T)18V) pursuant to our prior publications [20] instead of the kit's oligo dT. Moreover, a no-RT tube was prepared, including all materials needed for cDNA synthesis except reverse transcriptase enzyme.

**Primer design and quantitative real-time PCR:** In order to study the desired genes, we designed the specific primers by using Primer3 online software v4.1.0, synthesized by Metabolon, Germany. GAPDH and U6 genes were the internal control genes used in this study. The specific primers applied for HOTAIR, miR-331- 3p, GAPDH, and U6 expression evaluation are shown in Table 1**.** To ensure the accuracy of cDNA synthesis, RT-PCR was done by using specific primers, followed by Real-time PCR to investigate the gene expression changes using an Applied Biosystems (Massachusetts, USA) thermocycler. The PCR reaction volume for HOTAIR was 23 µl containing 1µl **(**1µg /µl) cDNA, 12 µl of 1X SYBR-Green master mix (Biofact, South Korea), 8µl of RNase-free water, 1µl of each specific forward and reverse primers (5 pm). The polymerase chain reaction program was as follows: initial denaturation at 95°C for 7 minutes, 40 cycles of denaturation at 94°C for 35 seconds, annealing at 59°C for 35 seconds, extension at 72°C for 35 sec, and a final extension step at 72°C for 7 minutes. The amplified fragment lengths were 159 bp and 235 bp for

HOTAIR and GAPDH, respectively, which were electrophoresed along with a 100 bp DNA ladder on 1.5% agarose gel containing safe stain. For miR-331-3p and U6, the final volume was 18µl containing 1 µl of cDNAs, 10µl of 1X SYBR-Green I master mix, 5µl RNase-free water, and 1µl(5 pm) of each primer. The PCR feature for miR-331-3p and U6 was as follows: Initial denaturation at 95°C for 7 min, 40 cycles of the second denaturation at 95°C for 30 sec, primer annealing at 60°C for 30 sec, and extension at 72°C for 30 sec, followed by 72°C for 5 min to final extension. The PCR products were 79 and 154 nt in length, respectively. The $2^{-\Delta\Delta Ct}$ method was used to quantify the relative levels of the studied gene's expression.

**Statistical analysis**

The results related to the expression level of HOTAIR and miR-331 genes were normalized by using the Kolmogorov–Smirnov test. All quantitative data were represented as means ± standard deviation (SD), and qualitative properties were investigated and shown as numbers (percentages). We utilized a T-test by SPSS v.19.0 software (SPSS, Chicago, IL, USA) in order to statistical analysis. Furthermore, we used the $2^{-\Delta\Delta Ct}$ method to estimate the expression fold changes of the desired genes, and figure plotting was performed by GraphPad Prism (version 7.05 for Windows, GraphPad Software, La Jolla, California, USA, www.graphpad.com). We considered p<0.05 as statistically significant.

## Results

In this research, 30 breast tumoral samples (case group) and 30 samples of the tumor's healthy margins (control group) were recruited to investigate the expression changes of miR-331-3p and HOTAIR genes in BC. Clinicopathological characteristics of the patients obtained from their hospital records are shown in Table 2.

After RNA extraction and cDNA synthesis, QRT-PCR was done. However, the expression of the studied genes, miR-331-3p and HOTAIR, illustrated significant differences between the case and control groups. So, statistical analysis showed that both the studied genes had higher expression levels in BC samples than in healthy specimens. Based on the findings, the expression amount of miR-331-3p in case and control groups was 2.8±0.34 vs 1.05±0.21, respectively, p<0.0001. Additionally, the relative expression and fold change of the studied genes were analyzed by using GraphPad Prism 7 software. As shown in Figures 1A and 1B, the expression level of miR-331-3p in the case group was about three times higher than that of the control group.

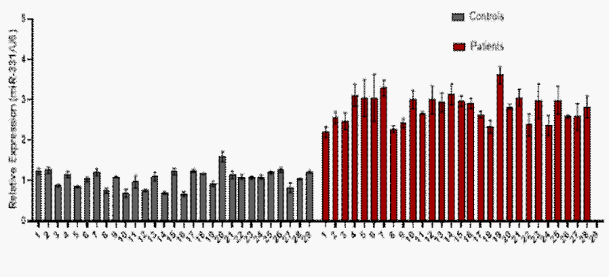


**Figure 1A:** Relative expression of miR-331-3p gene in each breast cancer and healthy sample.

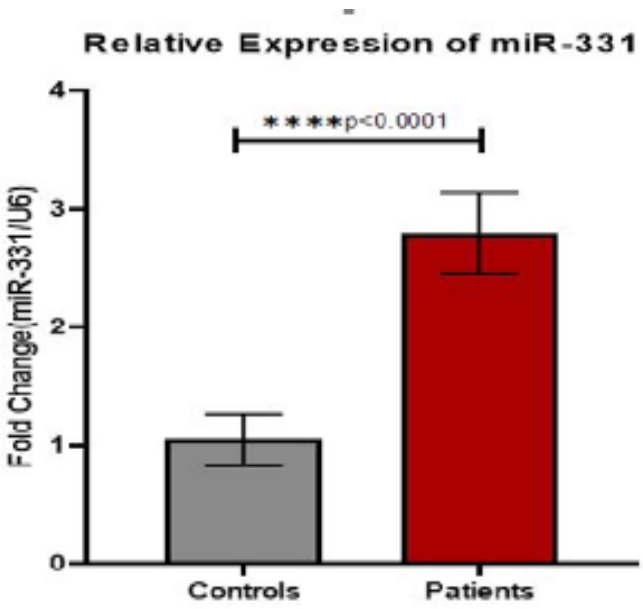


**Figure 1B:** Relative expression of the miR-331-3p gene in breast cancer patient and control groups. Results are the mean of three independent replicates. U6 was used as the reference gene.

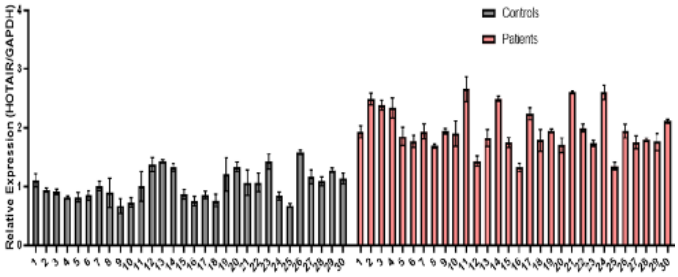


**Figure 2A:** Relative expression of the HOTAIR gene in breast cancer and control samples.

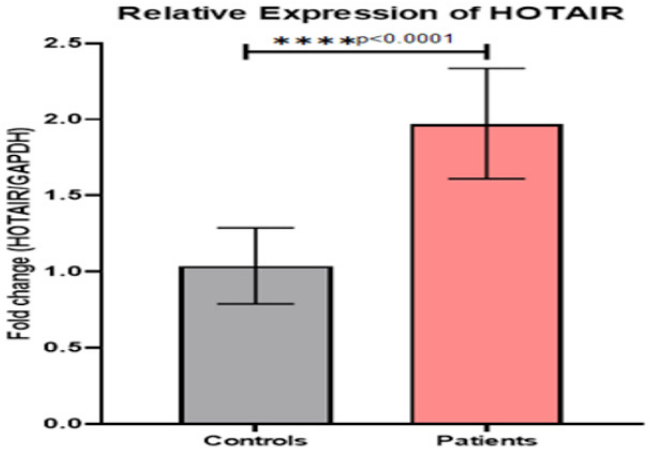


**Figure 2B:** Relative comparison of HOTAIR gene expression in breast cancer and healthy groups. GAPDH was used as a reference gene. Results are the mean of three independent replicates.

Also, HOTAIR expression level was 1.97±0.36 in BC samples vs 1.04±0.24 in normal samples, P<0.0001. Relative expression and fold change of the gene in the patient and control groups were computed. The results indicated that HOTAIR expression in the group of BC samples was almost twice compared to that in healthy samples of tumor margin tissues (Figures 2A and 2B).

**Table 1:** Details of the primers used in this research.

| Primer | Sequence | Product length (nt) |
|---|---|---|
| HOTAIR | F: 5'- GCC CAA ACA GAG TCC GTT-3'<br>R: 5'– CTACACACCCCCTCCGCTTC-3' | **159** |
| GAPDH | F: 5'– CATCACCATCTTCCAGGAGCG- 3'<br>R: 5'– GGAGGCATTGCTGATGATCTTG -3' | **235** |
| MIR-331-3p | F: 5'– GCCCCTGGGCCTATCC -3'<br>R: 5'– GCGTCGACTAGTACAACTCAAG -3' | **79** |
| U6 | F: 5'– CGGCAGCACATATACTAAAATTGG -3'<br>R: 5'– GCGTCGACTAGTACAACTCAAG -3' | **154** |

**Table 2:** Some clinical and pathological traits of the participants.

| Variables | **Mean ± SD / Number** (%) |
|---|---|
| Age (mean ± SD) | 52.84 ± 7.73 |
| Age of menarche (mean ± SD) | 12.66 ± 0.33 |
| Age of pregnancy (mean ± SD) | 23.51 ± 7.43 |
| BMI (mean ± SD) | 26.56 ± 9.88 |
| Oral contraceptive pills history<br>Yes<br>No | <br>12 (39%)<br>18 (61%) |
| Family history of breast cancer<br>Positive<br>Negative | <br>6 (20%)<br>24 (80%) |
| Menopausal status<br>Premenopausal<br>Postmenopausal | <br>10 (33%)<br>20 (67%) |
| Breastfeeding history<br>Positive<br>Negative | <br>23 (77%)<br>7 (23%) |
| Tumor site<br>Ductal | Right 10(33%)<br>Left 20 (67%) |
| Tumor size<br>≤ 2<br>>2 | <br>6 (20%)<br>24 (80%) |
| Estrogen Receptor<br>Positive<br>Negative | <br>26 (87%)<br>4 (13%) |
| Progesterone Receptor<br>Positive<br>Negative | <br>26 (87%)<br>4 13%) |
| Human Epidermal Growth Factor 2 (HER2)<br>Positive<br>Negative | <br>16 (53%)<br>14 (47%) |
| Tumor stage<br>0 – II<br>II – IV | <br>18(60%)<br>12 (40%) |

## Discussion

Breast Cancer (BC) is the most common cancer type in females in the world. Different factors are involved in breast cancer susceptibility and incidence, including genetic, epigenetic, and environmental factors. Identification of the molecular mechanisms of the disease can help in early diagnosis and effective treatment of breast cancer. Due to the growing occurrence of BC in Iran, for the first time, we studied the relationship between two important genes, miR-331-3p and HOTAIR, expression in women with breast cancer. In this case-control research, 30 women suffering from breast cancer were studied, and tumoral (case) and their adjacent normal tissue (control) samples were collected in order to investigate gene expression. Statistical analysis of the results showed significantly increased expression levels of both genes. As mentioned above, miR-331-3p and HOTAIR expression were almost three and two times, respectively, in the BC tumoral samples compared to the normal specimens.

Non-coding RNAs regulate many cell processes, including cell growth, differentiation, cell cycle, and Epithelial-Mesenchymal Transition (EMT). So, changed expression levels of their related encoding genes are a vital reason for cancerous cell features such as uncontrolled division, angiogenesis, and metastasis [11,21]. Diverse studies have been conducted on the relationship between microRNAs and breast cancer. A binary action miRNA, miR-331-3p, showed a pivotal role in cancer types, as an oncogene (e.g., AML, CML) [6] or tumor inhibitors such as glioblastoma and prostate, by participation in the cell signaling pathways [22]. There are various studies indicating a decreased amount of miR-331 expression in Colorectal and Ovarian Cancers (CRC), while it increased in pancreatic and cervical cancers [10,23]. While several studies revealed the relationship between miR-331 and some cancer pathologies, there are discrepancies in the reports about the miRNA and breast cancer association due to its expression changes. Some of them are consistent with our results, and others are in contrast to ours. In line with our findings, increased expression of miR-331-3p in malignant breast cancer has been shown, and its expression study may help in the discriminative diagnosis of benign and malignant BC [24], reported that the expression level of miR-331 in metastatic breast cancer patients is higher than in control individuals and promotes the disease [11]. Another study was done by, indicating significant upregulation of the microRNA in breast cancer tissues. Also, the research detected an association between high expression of miR-331 and some clinical and physiological characteristics, including lymph node metastasis, TNM stage, and poor prognosis, in line with [10,24]. Moreover, examined several miRNA expressions in BC patients to create a model for the recognition of different types of breast cancer using circulating microRNAs. Their study indicated that miR-331 expression was upregulated in breast cancer individuals and had an association with the disease stages and lymph node status [7]. Furthermore, suggested that miR-331 may be a hopeful marker in breast cancer diagnosis. Due to their findings, miR-331 has elevated expression in malignant breast cancer compared to the benign type of the disease [25]. However, some research is contrary to the suggestions and shows a decreased expression level of miR-331 in breast cancer, that denotates a tumor suppressor function for the microRNA. So determined significantly decreased expression of miR-331 in

Triple-Negative Breast Cancer (TNBC) patients, similar to the TNBC cell lines. Also, they found that the upregulated level of miR-331 is related to the reduction of malignancy in TNBC patients. On the other hand, elevated expression of the miRNA inhibits cancer promotion via targeting neuropilin-2 (NRP2), a receptor protein that is involved in different cell proliferation and angiogenesis that are dysregulated in cancer [22].

Moreover, Long Non-Coding RNAs (LNCRNAS) are related to many intra- and intercellular processes, including gene expression, metabolism, cell cohesion, and migration. It has been illustrated that LNCRNAS are more effective in microRNA expression and function [19,26], found that miR-331 is upregulated in BC tissues. They indicated that a lncRNA, an Anti-Differentiation Noncoding RNA (ANCR), inhibits breast cancer progression by miR-331 repression, showing that MIR is the target of the long noncoding RNA [27]. In line with our findings, increased expression of HOTAIR in breast cancer was reported by [17]. Also, a review paper reported that increased expression of HOTAIR is related to metastatic breast cancer and its clinical features [28]. Although HOTAIR and miR-331 have a key role in breast cancer, there is limited research on the relationship between them in breast cancer pathogenesis. published a review article suggesting that miR-331 elevation affects breast cancer via interaction with specific targets such as HER2, HOTAIR, and E2F1 [5], revealed that HOTAIR acts as a sponge to inhibit miR-331 in gastric cancer, causing cancer progression. The results of their research identified the tumor suppressor role of miR-331 in gastric cancer [13]. Additionally, reported that miR-331 acts as a HOTAIR suppressor in gastric cancer [6]. An opposite pattern of HOTAIR and miR-331 expression levels in cervical cancer was shown by [16]. In the study, a reduced amount of miR-331 was indicated despite other reports (16), examined HOTAIR′s role in gastric cancer. They found that HOTAIR and miR-331 have a negative correlation. The study indicated upregulation of miR-331 inhibits progression and metastasis in gastric cancer, indicating its inhibitory function, which is consistent with other studies that were done by [19,24]. HOTAIR acts as a competitive endogenous RNA for HER2 targeting by miR-331-3p. On the other hand, miR-331-3p has a tumor suppressor role in colon cancer, glioblastoma, and prostate cancer by reducing HER2 expression, leading to deactivation of the PI3/Akt signaling pathway [22,6]. It is worth noting that several factors are effective in miRNA-target interactions, such as compensatory transcriptional activation, intracellular compartment-specific expression patterns, and others.

## Conclusion

To our knowledge, this is the first study on the relationship between miR-331-3p and HOTAIR non-coding RNAs in breast cancer disease. Based on these research outcomes, the expression level of miR-331-3p and HOTAIR genes increased in breast cancer tumoral tissues compared to adjacent normal samples. Given that HOTAIR acts as a miR-331-3p sponge, leading to a reduction of the miRNA amount, our study demonstrated different results in breast cancer. However, it seems that miR-331-3p acts as a tumor suppressor in breast cancer, and an elevated amount of the miRNA may be against the high expression of HOTAIR. It may be the cell′s attempt to reduce the oncogenic effects of HOTAIR. However, more studies on a large number of participants are necessary in the future to identify breast cancer′s complicated molecular mechanisms. Also, our findings may help in breast cancer diagnosis and purposeful treatment.

## Declarations

**Conflicts of interest:** We declare there are no conflicts of interest in this work.

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