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The expression of the lncRNAs USP30-AS1, ELFN1-AS1, GAS8-AS1, and SNHG11 in breast cancer samples from Iranian patients from 2014 to 2019: a cross-sectional study

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Abstract

Objective Breast cancer is a widely prevalent and life-threatening malignancy that affects women worldwide. The identification of novel molecular markers associated with tumor progression is highly important for enhancing early detection, tailoring treatment approaches, and monitoring therapeutic outcomes. In this study, we investigated the expression patterns of four long noncoding RNAs (lncRNAs): USP30 antisense RNA1 (USP30-AS1), ELFN1 antisense RNA1 (ELFN1-AS1), GAS8 antisense RNA1 (GAS8-AS1), and small nucleolar RNA host gene 11 (SNHG11).

Results In breast cancer specimens, USP30-AS1 and GAS8-AS1 expression was decreased, whereas ELFN1-AS1 and SNHG11 expression was increased in breast cancer tissues compared with adjacent noncancer tissues. Decreased USP30-AS1 levels were associated with a smaller tumor size, lower tumor grade and stage, and the absence of lymphatic and vascular invasion. Lower GAS8-AS1 expression was associated with a lower tumor grade and positive estrogen and progestin receptor status. Elevated ELFN1-AS1 expression was associated with breast cancer that lacked P53 mutation. These changes suggest their promise as biomarkers for distinguishing between cancerous and noncancerous tissues.

Keywords Breast cancer, lncRNA, USP30-AS1, ELFN1-AS1, GAS8-AS1, SNHG11

Introduction

Breast cancer ranks as the second leading cause of cancer-related fatalities in women and is characterized by complex, multistage development that impacts various cell types [1, 2]. Even with notable advancements in cancer research, breast cancer remains a prominent public health issue and a primary focus of scientific investigation [3]. Therefore, in BC patients, early diagnosis can significantly affect mortality and reduce its rate in women [4].

Recent investigations in genomics and bioinformatics have revealed a substantial portion of noncoding RNA transcripts within eukaryotic genomes [5]. However, in

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recent years, their functional significance has attracted increasing interest from researchers [6].

lncRNAs are typically greater than 200 nucleotides in length and lack an open reading frame, rendering them incapable of encoding proteins [7]. lncRNAs can affect and control various stages of the cell cycle, such as progression, cell death, invasion, and migration [8].

The irregular expression of specific lncRNAs has been associated with increased cell proliferation, metastasis, epithelial–mesenchymal transition (EMT), suppressed apoptosis, adverse clinical outcomes, and invasion in patients with breast cancer [9]. Hence, the discovery and in-depth examination of pivotal lncRNAs with strong connections to breast cancer prognosis hold significant potential [10].

Research has indicated that a decrease in USP30-AS1 expression in colon cancer serves as an adverse predictor for prognosis and is linked with the progression of malignancy [11]. In contrast, USP30-AS1 was upregulated in LGG and GBM, with elevated expression in tissues of higher tumor grade compared with those with lower tumor grade [12]. studies have revealed an association between the invasiveness and growth capabilities of pancreatic cancer cells and the expression of the lncRNA ELFN1-AS1 [13]. A prospective target for therapeutic intervention may be ELFN1-AS1, given its role in promoting retinoblastoma progression through the regulation of the miR-4270/SBK1 pathway [14]. In papillary thyroid cancer (PTC), GAS8-AS1 functions as a tumor suppressor by restraining cell proliferation, inducing autophagy, and increasing ATG5 expression [15]. GAS8-AS1 can assume a tumor-suppressive function in colorectal cancer (CRC) through its control of the expression of the oncogenic lncRNA AFAP1-AS1 [16]. The malignancy driven by SNHG11 in colorectal cancer (CRC) is linked to alterations in YAP phosphorylation and overall YAP protein levels [17]. Recognizing SNHG11 as a potential target for therapy and a prognostic marker has the potential to enhance the care of patients with colorectal cancer (CRC) [18].

Considering the roles of the lncRNAs ELFN1-AS1, GAS8-AS1, SNHG11, and USP30-AS1 in tumor growth, survival, and metastasis, further scrutiny of their expression has potential for gaining a more precise understanding of their involvement in breast cancer. Unraveling the underlying mechanisms of cancer is pivotal for crafting effective therapies, and fine-tuning the levels of these lncRNAs on the basis of their interactions with target molecules and their impacts on cancer-related pathways can aid in elucidating the mechanisms of tumor growth. Furthermore, variations in gene expression between healthy and affected tissues can serve as diagnostic markers, whereas disparities in expression levels across different tumor grades can shed light on the relationship between these genes and disease prognosis. As such, this study aimed to explore the expression of these genes and their connections with clinicopathological parameters in patients with breast cancer.

Table 1 Demographic characteristics of patients

Parameters	Patients group *n*/d (%)
Age (years)	
< 50	16 (40.0)
≥ 50	24 (60.0)
Race	
Persian	9 (22.5)
Azari	13 (32.5)
Gilaki and Mazani	4 (10.0)
Kurd	4 (10.0)
Lor	3 (7.5)
Unknown	7 (17.5)
Stage	
I-II	29 (72.5)
≤ III	11 (27.5)
Histology grade	
Grade I (low-well differentiated)	4 (10.0)
Grade II (intermediate-moderately	22 (55.0)
differentiated)	14 (35.0)
Grade III (high-poor differentiated)	
Tumor size (cm)	
< 5	25 (62.5)
≥ 5	15 (37.5)

Materials and methods

Patient selection and sample collection

Our research is based on a cross-sectional case–control investigation involving 40 breast cancer tumor samples and noncancerous group was derived from the adjacent tumor margin for each sample, tissues sourced from the Cancer Institute at Imam Khomeini Hospital, Tehran, Iran. The average age of the patients studied was 52 years, with a median age of 52.5 years. Additionally, the average tumor size among the patients was 6.4 cm, with a median size of 4.0 cm. The sample size was determined on the basis of a study by Yang et al. [19]. All participants were treatment-naïve breast cancer patients who underwent primary surgery. The exclusion criteria included prior medical conditions, medication usage, and previous therapeutic interventions. The surgeon procured samples of both cancerous and adjacent noncancerous breast tissues during surgery. These samples were promptly frozen in liquid nitrogen and stored at -80 °C in the tumor repository.

A portion of the tissue was subsequently placed in 10% formalin for histopathological analysis. The demographic details of the patients were documented and archived within the tumor repository, as depicted in Table 1.

Tissue sample RNA extraction and DNase treatment

First, the frozen tissue samples were pulverized with liquid nitrogen via a mortar and pestle. Total RNA was subsequently extracted from each sample following the manufacturer's protocol for RiboExTM (Gene All, Korea). The collected RNA was then preserved at -70 °C for subsequent cDNA synthesis. The extracted RNA was subjected to electrophoresis on an agarose gel for quality evaluation, and the quantity was determined via a NanoDrop spectrophotometer. For DNase treatment, the DNasel RNase-free Kit (Sinaclon, Iran) was used in accordance with the manufacturer's instructions.

Extraction of RNA from tissue for cDNA synthesis

In this study, cDNA was generated from mRNA following the guidelines provided by the manufacturer of the cDNA Synthesis Kit (Yekta Tehiz Azma, Iran).

Quantification of USP30-AS1, ELFN1-AS1, GAS8-AS1, and SNHG11 gene expression

We assessed the expression levels of the USP30-AS1, ELFN1-AS1, GAS8-AS1, and SNHG11 genes via quantitative SYBR green master mix (Ampliqon; Denmark) in conjunction with the Applied Biosystems system (USA). The expression of hypoxanthine phosphoribosyl transferase 1 (HPRT1), a reference gene, was used. The specific primer sequences for these genes can be found in Table 2.

Quantitative PCR (QPCR)

For each qPCR, a mixture of 0.3 µL of each primer (0.8 µM, final concentration), 6.25 µL of SYBR Green master mix, and 0.5 µL of cDNA (10 ng) was combined to achieve a final volume of 12 µL with distilled water. These reactions were carried out in duplicate via a LightCycler 96 system (USA). The PCR cycling conditions were as follows: initial enzyme activation for 15 min at 95 °C, followed by 40 cycles of 15 s at 95 °C and 60 s at 60 °C. A linear heating phase from 60 to 95 °C was executed to generate a melting curve. The relative fold change for each gene in malignant samples relative to their respective controls was determined via the following formula:

Delta Ct = Ct Gene – Ct HPRT.

Delta Delta Ct = ΔCt cancer tissue – ΔCt control.

Fold change = $2^{-(\Delta CT \text{ cancer tissue} - \Delta CT \text{ control})}$.

The PCR efficiency for the genes was checked via LinReg PCR software, efficiency values for USP30-AS1, ELFN1-AS1, GAS8-AS1, and SNHG11 primers were 93%, 93%, 93% and 93%, respectively, and 98% for HPRT primer. Based on primer efficiency, the reaction efficiency values for CASC2, NEAT1, LINC00299 and HPRT were calculated by the formula (E = 1 + primers efficiency) equal to 1.93, 1.93, 1.93, 1.93 and 1.98, respectively. Considering that the reaction efficiency values for all four genes are between 1.9 and 2, the $2^{-\Delta\Delta Ct}$ formula was suitable to measure the fold change of each gene.

Table 2 Specifications of the primers used

Genes	Forward primer (5′->3′)	Reverse primer (5′->3′)	Product length
USP30-AS1	CCAGAGTGGAAATAGGTCGCA	GGCACCCAAGTAAACAATAAGT	143
ELFN1-AS1	ACCATCCGCCACATTCCTAC	GCAGGTGGATTAGATGCTGC	104
GAS8-AS1	CAACGAGCAAACAAGAAGGAG	TGAGCCAAACAGACCAGTCA	188
SNHG11	TGGGAGTTGTCATGTTGGGA	ACTCGTCACTCTTGGTCTGT	196
HPRT	CCTGGCGTCGTGATTAGTG	TCAGTCCTGTCCATAATTAGTCC	125

Statistical analysis

To assess data normality, the Kolmogorov–Smirnov test was applied. Given that the data for all four genes deviated from a normal distribution, nonparametric tests, specifically the Mann–Whitney test and Kruskal–Wallis test, were employed for group comparisons. Data analysis was conducted via SPSS22 software and GraphPad Prism 9. Additionally, the interplay between genes was scrutinized via Spearman's correlation coefficient. Significance was established at a p value less than 0.05.

Results

Breast cancer diagnosis was histologically verified by a pathologist, and total RNA was extracted from recently frozen tissue samples. The gene expression levels of USP30-AS1, ELFN1-AS1, GAS8-AS1, and SNHG11 were subsequently quantified via quantitative RT–PCR (QPCR) after cDNA synthesis.

Differences in USP30-AS1, ELFN1-AS1, GAS8-AS1 and SNHG11 expression between the control and cancer groups

Analysis of 40 paired samples via QPCR revealed a significant 4.5-fold increase in USP30-AS1 gene expression in adjacent nonmalignant tissues compared with that in malignant breast tissues ($P < 0.02$, as depicted in Fig. 1a). An examination of ELFN1-AS1 expression levels in malignant breast tissues versus adjacent nonmalignant tissues revealed a notable 2.9-fold increase in ELFN1-AS1 expression in the breast cancer samples ($P < 0.02$, as illustrated in Fig. 1-b). A pronounced reduction (2.6-fold) in GAS8-AS1 expression was evident in cancerous breast tissue compared with adjacent nonmalignant tissue ($P < 0.04$, as visualized in Fig. 1-c). The RNA expression of SNHG11 was 2.6-fold greater in malignant breast tissue than in adjacent nonmalignant tissue ($P < 0.001$, as depicted in Fig. 1-d).

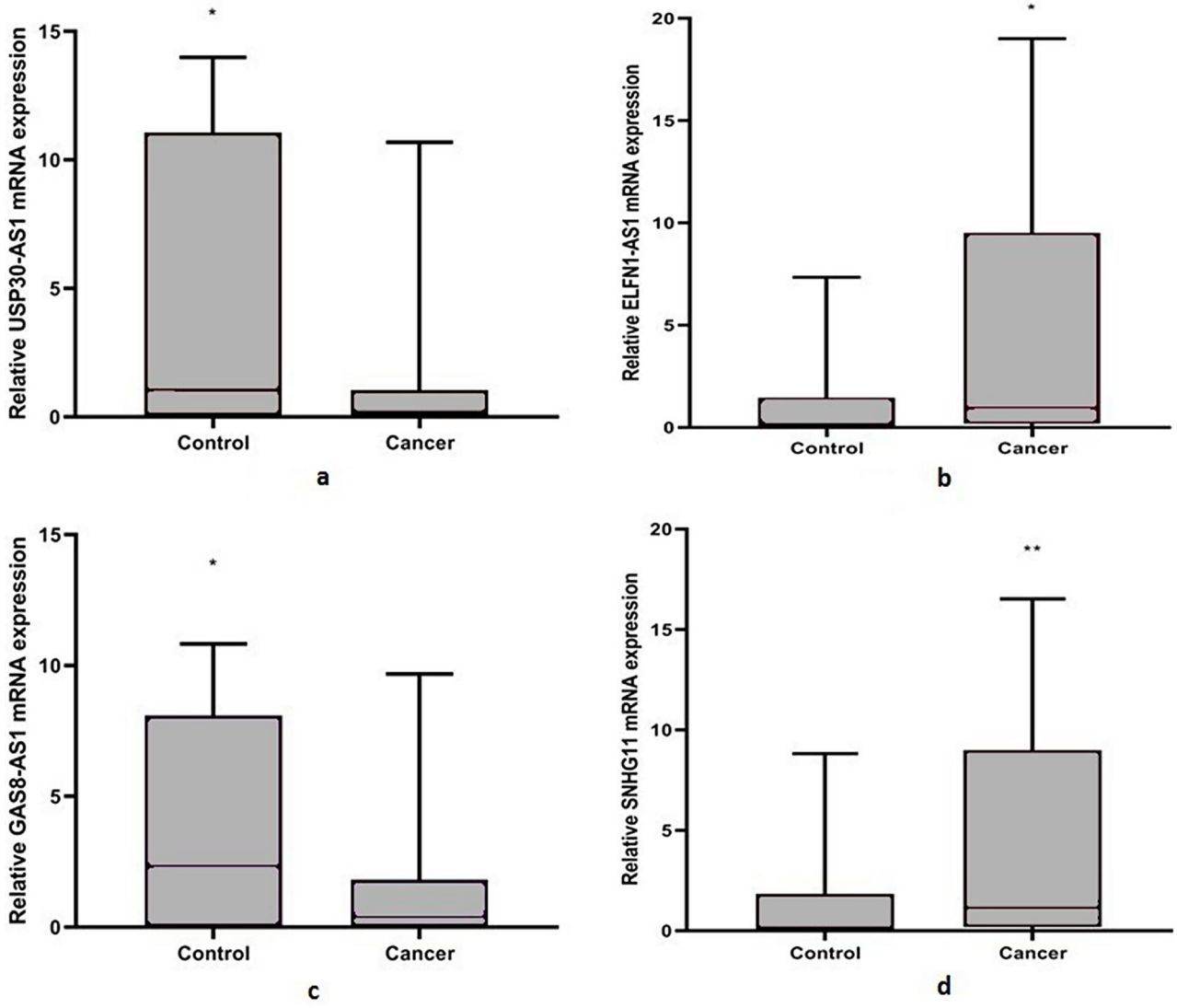

Fig. 1 Comparative analysis of the gene expression of USP30-AS1, ELFN1-AS1, GAS8-AS1, and SNHG11 in the control and cancer groups. Panel **a** shows the contrast in USP30-AS1 gene expression between the control and cancer groups. The results are presented as medians (with maximum and minimum values), utilizing HPRT as a reference gene (*$P < 0.0295$ in comparison with the nontumor group). In Panel **b**, the comparison of ELFN1-AS1 gene expression between the control and cancer groups is shown, reported similarly to the medians (maximum and minimum values), with HPRT as the reference gene (*$P < 0.0258$ compared with the nontumor group). Panel **c** shows the comparison of GAS8-AS1 gene expression between the control and cancer groups, again reported as medians (maximum and minimum values), with HPRT as the reference gene (*$P < 0.0414$ compared with the nontumor group). Finally, Panel **d** shows the comparison of SNHG11 gene expression between the control and cancer groups, with the results expressed as medians (maximum and minimum values) and HPRT as the reference gene (**$P < 0.0046$ compared with the nontumour group). Each graph presents the medians, maximum and minimum gene expression levels across 40 breast cancer samples and their corresponding 40 control samples

Relationships between USP30-AS1, ELFN1-AS1, GAS8-AS1, and SNHG11 expression and clinicopathological parameters in breast cancer patients

By using SPSS software to evaluate the associations between USP30-AS1 gene expression and the clinicopathological attributes of patients, a noteworthy observation was made. USP30-AS1 expression was significantly increased in tumors characterized by smaller size, lower grade, earlier stage, and an absence of lymphatic or vascular invasion ($P<0.05$). Nevertheless, no substantial correlation was detected between USP30-AS1 expression and other clinicopathological features ($P>0.05$, as detailed in Table 3). Furthermore, assessment of the associations between ELFN1-AS1 gene expression and various clinicopathological parameters revealed a conspicuous increase in ELFN1-AS1 gene expression in tumors lacking the P53 protein ($P<0.05$). Nevertheless, no substantial correlation was observed between ELFN1-AS1 expression and other clinicopathological features ($P>0.05$, as depicted in Table 3). An examination of the associations between GAS8-AS1 gene expression and various clinicopathological factors in patients revealed

Table 3 Association between USP30-AS1, ELFN1-AS1, GAS8-AS1, and SNHG11 expression and clinicopathological characteristics in breast Cancer

Variable	USP30-AS1		ELFN1-AS1		GAS8-AS1		SNHG11	
	p-value	Maximum Median Minimum	p-value	Maximum Median Minimum	p-value	Maximum Median Minimum	p-value	Maximum Median Minimum
Tumor size (cm)	0.007	13.68	0.58	11.74	0.83	10.82	0.98	16.52
< 5		0.91		0.83		0.28		0.42
		0.00		0.00		0.00		0.00
≥ 5		13.99		19.01		7.60		12.27
		0.07		0.29		0.73		0.33
		0.01		0.01		0.00		0.00
Grade	0.004	13.99	0.65	5.54	0.003	9.88	0.57	10.23
I		6.70		0.19		6.60		0.37
		1.14		0.00		0.49		0.00
II		13.68		16.42		10.82		16.52
		0.08		0.96		1.08		0.31
		0.01		0.00		0.00		0.00
III		8.31		19.01		9.69		12.58
		0.36		0.41		0.79		0.72
		0.00		0.00		0.00		0.00
Stage	0.002	13.99	0.18	13.52	0.16	10.82	0.65	16.52
I-II		1.04		0.24		0.90		0.36
		0.00		0.00		0.01		0.00
III≤		10.69		19.01		6.09		10.85
		0.07		0.95		0.17		1.13
		0.01		0.01		0.00		0.02
ER	0.08	13.91	0.85	13.59	0.01	10.82	0.60	12.58
Positive		0.73		0.39		0.53		0.34
		0.00		0.00		0.01		0.00
Negative		10.69		19.01		6.67		12.27
		0.16		0.21		0.05		1.04
		0.00		0.02		0.00		0.00
PR	0.05	13.91	0.30	9.68	0.03	10.82	0.49	10.85
Positive		0.87		0.18		0.42		0.34
		0.00		0.00		0.01		0.00
Negative		10.69		11.74		6.67		12.58
		0.30		0.22		0.41		1.04
		0.00		0.00		0.00		0.00
P53	0.58	13.91	0.04	10.13	0.63	5.61	0.83	10.23
Positive		0.65		0.11		0.04		0.23
		0.01		0.02		0.02		0.00
Negative		10.92		13.52		4.24		10.85
		0.17		0.91		0.12		0.27
		0.01		0.18		0.01		0.02

Table 3 (continued)

Variable	USP30-AS1		ELFN1-AS1		GAS8-AS1		SNHG11	
	p-value	Maximum Median Minimum	p-value	Maximum Median Minimum	p-value	Maximum Median Minimum	p-value	Maximum Median Minimum
Necrosis	0.65	13.99	0.82	19.01	0.08	9.69	0.27	16.52
Yes		0.24		0.53		0.28		0.36
		0.00		0.00		0.00		0.00
No		13.91		12.58		10.82		12.58
		0.23		0.69		1.74		0.69
		0.01		0.00		0.00		0.00
Lymphatic invasion	0.01	13.91	0.23	19.01	0.21	10.82	0.66	12.58
Yes		0.13		0.82		0.26		0.36
		0.00		0.00		0.00		0.00
No		13.99		10.13		10.51		16.52
		1.19		0.18		2.68		0.43
		0.02		0.00		0.00		0.00
Vascular invasion	0.01	13.91	0.23	19.01	0.21	10.82	0.66	12.58
Yes		0.13		0.82		0.26		0.36
		0.00		0.00		0.00		0.00
No		13.99		10.13		10.51		16.52
		1.19		0.18		2.68		0.43
		0.02		0.00		0.00		0.00

that GAS8-AS1 expression was significantly increased in tumors with lower grades and negative estrogen and progesterone receptor results, as detailed in Table 3 ($P<0.05$). Nonetheless, no significant correlation was found between GAS8-AS1 expression and other clinicopathological features ($P>0.05$). For SNHG11 RNA expression, no significant associations were identified with clinicopathological features ($P>0.05$, as outlined in Table 3).

Discussion

The findings of this study revealed a decrease in USP30-AS1 expression in malignant breast tissue compared with adjacent nonmalignant tissue ($P<0.02$, Fig. 1-a).

Moreover, an exploration of the relationships between USP30-AS1 expression levels and various clinicopathological characteristics of breast cancer tissues revealed a significant increase in USP30-AS1 expression in tumors characterized by smaller size, lower grade, earlier stage, and the absence of lymphatic and vascular invasion (as depicted in Table 3), with statistical significance ($P<0.05$). These findings suggest a potential role for USP30-AS1 as a tumor suppressor [11].

Chengren Li and colleagues conducted a study investigating the role of USP30-AS1 in colon cancer tissue. These findings highlight the potential therapeutic importance of USP30-AS1 in managing colon cancer [11].

In 2021, a study by Mengyue Chen and colleagues revealed novel insights into the association between USP30-AS1 expression and the overall survival of cervical cancer patients. These findings indicated that higher levels of USP30-AS1 were significantly linked to a poorer overall survival rate in this patient population [20]. Moreover, it could be investigated as a novel avenue for targeted therapy in the future, offering promising prospects for the management of cervical cancer [20].

Our findings revealed a significant 2.9-fold increase in the expression level of the lncRNA ELFN1-AS1 in malignant breast tissue compared with that in adjacent nonmalignant tissue ($P<0.02$, as illustrated in Fig. 1-b). Additionally, our examination of the associations between ELFN1-AS1 gene expression and various clinicopathological features of patients revealed substantial upregulation of ELFN1-AS1 expression in tumors lacking P53 protein ($P<0.05$, as demonstrated in Table 3). In 2020, Youkun Jie and colleagues reported their findings, which suggested that ELFN1-AS1 plays a role in enhancing cell proliferation, migration, and invasion through the miR-497-3p/CLDN4 pathway in ovarian cancer (OV). This research underscores the potential importance of ELFN1-AS1 in the context of ovarian cancer, offering insights into its function in cell behavior and its interaction with specific molecular pathways [21]. Therefore, these results indicate that ELFN1-AS1 holds promise as a potential diagnostic biomarker and a therapeutic target for ovarian cancer [21].

A significant 2.6-fold reduction in GAS8-AS1 expression was evident in malignant breast cancer tissues compared with adjacent nonmalignant tissues ($P<0.04$, as depicted in Fig. 1-c). Furthermore, examination of the associations between GAS8-AS1 gene expression and various clinicopathological features of patients revealed a notable increase in GAS8-AS1 gene expression in lower-grade tumors and tumors lacking estrogen and progesterone receptors (with a significance level of $P<0.05$, as indicated in Table 3). In 2018, Wenting Pan and colleagues reported that the lncRNA GAS8-AS1 plays a crucial role in maintaining the GAS8 promoter in an accessible chromatin conformation. These findings shed light on the potential regulatory function of GAS8-AS1 and its impact on gene expression in various cellular contexts [22]. Hence, it is reasonable to propose that lncRNA GAS8-AS1 is involved in a surveillance mechanism that safeguards the activation of the GAS8 promoter and transcription, thereby acting as a preventive measure against carcinogenesis [22].

A noticeable 2.6-fold increase in SNHG11 RNA was detected in malignant breast tissue compared with adjacent nonmalignant tissue ($P<0.001$, as illustrated in Fig. 1-d). However, there was no significant correlation between SNHG11 RNA expression and clinicopathological features ($p>0.05$, as detailed in Table 3).

In 2020, Wei Huang and colleagues employed a llncRNA microarray assay and RT−PCR analysis to reveal the upregulation of SNHG11 expression in hepatocellular carcinoma (HCC) tumor tissues and HCC cells. Their research also revealed a link between increased SNHG11 expression and decreased survival rates among HCC patients [23]. In 2020, a study conducted by Weizhen Huang and colleagues revealed that elevated SNHG11 expression served as an indicator of an unfavorable prognosis for patients diagnosed with colorectal cancer (CRC) [20]. Huang and colleagues reported that SNHG11 promotes the proliferation of colorectal cancer (CRC) cells by directly interacting with IGF2BP1, leading to the stabilization of c-Myc mRNA. This, in turn, facilitates the transcriptional upregulation of SNHG11. Therefore, the reciprocal regulation of SNHG11 and c-Myc assumes a central role in driving cell proliferation in CRC [24].

Taken together, the results of this study revealed the downregulation of USP30-AS1 and GAS8-AS1, along with the upregulation of ELFN1-AS1 and SNHG11, in breast cancer tissues compared with adjacent noncancerous tissues ($P<0.05$). Nevertheless, comprehensive research is warranted to elucidate the functions of these lncRNAs in the onset and progression of breast cancer. Furthermore, these genes have the potential to function

as biomarkers for distinguishing cancerous tissue from noncancerous breast tissue.

Limitations

The limitations of this article include not having normal tissue from a normal person, financial limitations, and the insufficient number of samples so that comparisons between subgroups can be made.

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Not applicable.

Author contributions
Maryam Adelipour and Ghazal Orak contributed to the study design, data collection and manuscript preparation; Fereshteh Ameli contributed to sample collection; Zahra Orak Chahartangi and Zahra Nazeri contributed to the literature search and data collection. All the authors contributed to critically revising the manuscript for important intellectual content, read and approved the final version submitted for publication, and take responsibility for the statements made in the published article.

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Data availability
The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate
The research conducted in this study obtained approval from both the Medical Ethics Committee of the Cancer Institute at Imam Khomeini Hospital (RA) and the Medical Ethics Committee of Jundishapur University of Medical Sciences (Ethical ID: IR.AJUMS.REC.1401.548). Furthermore, the study was conducted in compliance with the principles set forth in the Declaration of Helsinki and clinical practice guidelines. All volunteers signed informed consent forms.

Consent for publication
Not applicable.

Transparency statement
The lead author Maryam Adelipour affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Competing interests
The authors declare no competing interests.

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