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ASSESSMENT OF ALPHA-L-FUCOSIDASE AND FUCOSYLTRANSFERASE- 4 ENZYMES IN HEALTHY AND TUMOR TISSUES OF PATIENTS WITH BREAST CANCER

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Abstract – *Objective:* *Breast cancer is the most prevalent cancer and is one of the most common causes of cancer-related deaths among women. Although the fucosylation process is essential for normal biological functions, dysregulation of the fucosylation level may be involved in cancer and increasing its metastatic capacity. For this purpose, we evaluated the status of Fucosyltransferase-4 (FUT4) and Alpha-l-fucosidase (AFU) enzymes in healthy and tumor tissues of patients with breast cancer.*

Materials and Methods: *In this study, the levels of FUT4 and AFU were evaluated in 33 tumor tissues and matched adjacent tissue samples of breast cancer patients using the ELISA. Also, these levels were measured in the early and advanced stages of the disease.*

Results: *The results revealed that the tissue level of FUT4 in the tumor group was significantly higher than healthy ones, while there was no statistically significant relationship between its level changes and other clinicopathological features of tumor. Moreover, the AFU investigation showed a statistically significant relationship between its level with different stages and grades of the tumor, as well as lymph node involvement. Whereas, no significant differences observed in AFU level between tumor tissues and health y ones.*

Conclusions: *The present study revealed that alterations in FUT4 and AFU levels may be involved in pathogenesis and progression of breast cancer. Therefore, investigation of their pathogenesis pathways in future studies may be helpful in the early diagnosis of breast cancer, prevention of its progression, as well as its therapeutic applications. Also, further and larger-scale studies are needed to confirm these findings.*

KEYWORDS: *Breast Neoplasms, FUT4 protein, Alpha-L-Fucosidase.*

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INTRODUCTION

Breast cancer is the most prevalent cancer and is one of the most common causes of cancer-related deaths among women[1]. The disease is less prevalent in men compared to women and accounts for only 1% of all breast cancer cases[2,3]. Most breast cancer deaths caused by recurrence and distant metastasis of the primary tumor, whereas its early diagnosis and treatment result in a relatively better outcome. Therefore, the identification of early diagnostic and therapeutic markers can improve these patients' survival rates[4]. Regarding this issue, many researchers have focused on finding highly sensitive and specific markers for early detection of breast cancer[5]. Glycosylation is one of the essential post-translational events that affect the physical and chemical properties, as well as the structure and function of proteins. The studies on various cancers have shown that dysregulation of glycosylation is related to proliferation, metastasis, and prognosis of cancer[4]. Fucosylation is one of the most common glycosylation events in the body, which catalyzes the transfer of fucose (6-deoxy-L-galactose) to oligosaccharide and protein chains. This process regulates by various types of factors, such as fucosyltransferases (FUTs), GDP-fucose synthase and GDP-fucose transporter[6,7]. Although the fucosylation process is critical for normal biological function, the changes that occur at its level can contribute to the development of cancer and increase its metastatic capacity[8] Fucosylation level is dependent on the function of FUTs and Alpha-L-fucosidase (AFU) in different tissues or cells[9].

The FUT family is a group of enzymes that catalyze the transfer of L-fucose from GDP-beta-L-fucose to different acceptor molecules, such as N-acetyl lactosamine[10]. According to the fucosylation site, there are different FUTs[11]. FUT_4 is one of the α1,3-fucosyltransferases (EC: 2.4.1.152), which catalyzes the transfer of L-fucose to the sugar chains of glycoproteins at 1 and 3 sites. An abnormal elevation of FUT_4 and its synthetic product, Lewis Y (LeY), has been identified in various cancers (Figure 1)[4,12]. The past researches have shown that FUT_4 and LeY are positively regulated in breast cancer and promote epithelial-mesenchymal transition (EMT) through activation of phosphatidylinositol 3-kinase (PI3K) / Akt- glycogen synthase kinase 3-beta (GSK3B) and mitogen-activated protein kinase (MAPK(/ nuclear factor-kB)NF-kB(signaling, which it is also an essential step in tumor progression[13,14]. Therefore, it is expected that defucosylation improved this condition. However, some studies have claimed that defucosylation leads to the escape of tumors from natural killer (NK) cells and get more malignancy[7]. AFU is a lysosomal glycosidase enzyme (EC: 3.2.1.51) that plays a role in the degradation of terminal fucose[9,15,16].

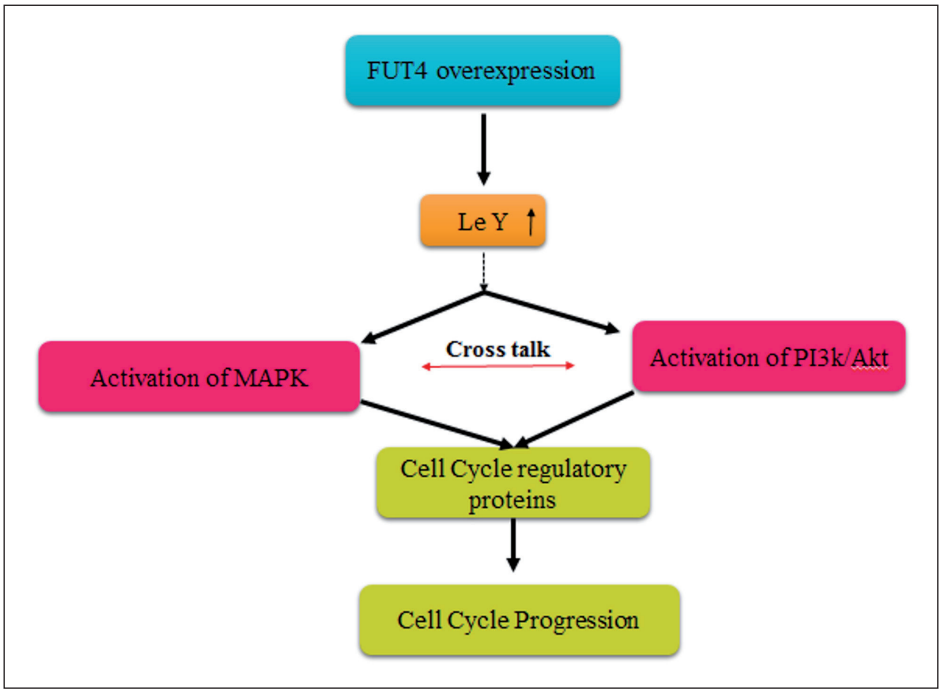

Fig. 1. Effect of FUT4 on cell cycle through activation of PI3K / Akt and MAPK signaling pathways.

According to this information, there may be a relationship between these enzymes and breast cancer. Therefore, due to the lack of information in this field and the inconsistencies between the results of different studies, further investigation is needed. In this study, we aimed to evaluate the status of FUT_4 and AFU enzymes in healthy and tumor tissues of breast cancer patients using the enzyme-linked immunosorbent assay (ELISA) technique.

Further efforts are required to achieve a greater understanding of biomarkers' role in human cancer. We believe that this will contribute to the development of future research in the mechanism of biomarker in order to improve the quality of patient's life with cancer. In our ongoing research projects on the human cancer mechanism, we undertook the present project.

MATERIALS AND METHODS

Tissue samples collection

In this prospective case-control study, 45 fresh-frozen tissues of breast cancer and matched adjacent noncancerous tissues were obtained from women with breast cancer at the Affiliated Hospital of Babol Medical University (Babol, Iran). The 33 pairs of samples were selected based on our inclusion and exclusion criteria. Exclusion criteria included patients with other cancers and malignancies, patients who received other pre-surgical treatments such as chemotherapy and radiotherapy, and diabetic patients. The samples were collected with the consciously written consent of patients and after approval by the Ethics Committee of Babol Medical University (IR.MUBABOL.HRI.REC.1397.131). Also, demographic and complementary data were obtained through questionnaires, and clinicopathological findings were recorded after surgery. The tumor samples were classified into two groups of early (0-2) and advanced (3) stages based on the TNM classification system. The collected samples transferred to -80°C freezer by a nitrogen tank and kept there until the collection was complete.

Preparation of samples

The collected samples were excluded from -80°C freezer and kept at room temperature for 10-15 minutes. The same weights of samples were obtained and mixed with equal volumes of PBS (pH 7.4) containing an antiprotease cocktail (Sigma-Aldrich, St. Louis, MO, USA). Afterward, samples were homogenized using an ultrasonic homogenizer (BANDELIN, Berlin, Germany), and the milky solution was formed. All steps were performed on the ice to provide the appropriate temperature and prevent adverse effects on these enzymes. In the following and according to the kit instructions, the milky solution obtained in the previous step was centrifuged at 3000 RPM and 4°C for 20 minutes. Then, the supernatants were collected and aliquot into separate microtubes, and finally transferred to -20°C until subsequent steps.

Measurement of total protein by the Bradford method

Total Protein of tissue samples was determined using the Bradford Protein Assay Kit and according to the kit manufacturer's instructions (DNA Biotech., Tehran, Iran). The results were read with an ELISA Reader machine (Titertek-Berthold, Pforzheim, Germany) at 595 nm, and the concentration of unknown proteins was determined using the standard curve of BSA.

Measurement of Fucosyltransferase 4 and Alpha-l-fucosidase enzymes

The samples and kit contents were naturally warmed up to room temperature. Then, samples were thoroughly mixed, and tissue levels of FUT_4 and AFU enzymes were determined using human ELISA kits (Bioassay Technology Laboratory, Shanghai, China). Finally, the results were read by an ELISA Reader machine (Titertek-Berthold, Pforzheim, Germany) at 450 nm, and the concentrations of these enzymes were determined using the standard curve.

Statistical analysis

All statistical analyses were done using SPSS software version 20 (SPSS Inc., Armonk, NY, USA), and results reported as the mean ± SEM. Initially, the Shapiro-Wilk test used to examine the normal distribution of data, and results revealed abnormal distribution in both groups (non-parametric). Therefore, multiple comparisons of data performed using non-parametric statistical tests, such as Wilcoxon, Mann-Whitney, and Kruskal-Wallis, and p-value < 0.05 was considered statistically significant. In addition, Receiver operating characteristic (ROC) curves were plotted to estimate the sensitivity and specificity of the tests and to determine the optimal cutoff values for these enzymes. The cutoff value selected was the point with the highest sensitivity and specificity.

RESULTS

Demographic and clinicopathological features of patients

In this study, the levels of FUT_4 and AFU in 33 tumor tissues and matched adjacent tissue samples of breast cancer patients were evaluated using ELISA. The mean age of the patients at diagnosis was 52.09 ± 1.65 years (Age range: 33–79). The demographic and clinicopathological features of patients are shown in Tables 1 and 2, respectively.

Comparison of FUT_4 and AFU levels between healthy and tumor tissues of patients with breast cancer

A Wilcoxon statistical test was used to compare the levels of FUT_4 and AFU enzymes between the tumor tissues and healthy ones. These results revealed that the mean level of FUT_4 in tumor tissues was significantly higher than healthy ones, while there was no statistically significant difference in the AFU level between these groups (Table 2, Figures 2a and 2b).

The relationship between FUT_4 and AFU levels with clinicopathological features of patients

This part of the study involves comparing the tissue-level changes of FUT_4 and AFU enzymes between the early and advanced stages of the disease, different histological tumor grades, tumor sizes, as well as the number of lymph nodes involved. The Mann-Whitney statistical test used to compare these changes in the early and advanced stages of the disease. The results showed no significant difference in the FUT_4 level between early and advanced stages of the disease, while the AFU level at the early stages was significantly higher than the advanced stages (Figures 3a and b). Also, the Kruskal-Wallis statistical test used to evaluate the relationship between levels of FUT_4 and AFU with other clinicopathological features. The results revealed no significant statistical relationship between the FUT_4 level and clinicopathological features of tumor. Moreover, no significant difference was observed in the AFU level among different tumor sizes, while there was a statistically significant relationship between AFU level and histological tumor grades or lymph nodes involvement, such that its level in grade 2 and N0 was significantly higher than grade 3 and N1, respectively.

The diagnostic value of FUT_4 level for differentiating tumor group from healthy ones

In this present study, the ROC curve and area under the curve (AUC) used to determine the diagnostic value of the FUT_4 level to differentiate the tumor group from healthy ones. According to this analysis, a cutoff value of 10.929 revealed the best diagnostic accuracy for distinguishing the tumor group from the healthy ones: AUC= 0.626 (95%; CI= 0.491-0.761); sensitivity= 57.6 %; specificity= 66.7% (Figure 4).

DISCUSSION

Breast cancer is one of the most common cancers among women[1]. Approximately 90% of these deaths are due to the recurrence and distant metastasis of the primary tumor, while its early diagnosis and treatment can lead to better results[4]. Regarding this issue, it is very necessary to find highly sensitive and specific markers for the early detection of breast cancer[5]. Fucosylation is one of the most important glycosylation events that oc-

TABLE 1. Demographic characteristics of patients.

Variable		*Number*	*Percentage*
Age average (Year)	52.09± 1.65	33	-
Age range (Year)	30-49	13	% 39.4
	50-80	20	% 66.6
Marital status	Single	1	% 3
	Married	32	% 97
Family history	+	6	% 18.2
	-	27	% 81.8
Breast side involved	Left	16	% 48.5
	Right	17	% 51.5

TABLE 2. Relationship between FUT4 and AFU levels with clinicopathological features of patients.

Variable (Clinicopathological features)			*Number*	*Percentage*	*Mean Ranks*		*Mean ± SEM (Median)*		*p-value*	
					FUT4	*AFU*	*FUT4*	*AFU*	*FUT4*	*AFU*
Tumor size	T1		19	% 57.6	17.47	19.16	14.569±2.730 (13.838)	205.539±41.366 (175.558)	0.637	0.223
	T2		12	% 36.4	15.42	15.00	12.472±2.688 (13.949)	143.173±34.613 (130.436)		
	T3		2	% 6.1	22.00	8.50	16.922±12.863 (16.922)	69.506±46.057 (69.506)		
Lymph nodes involved	N0		13	% 39.4	19.08	23.00	16.559±2.874 (16.369)	265.797±49.067 (266.758)	0.065	0.026
	N1		12	% 36.4	11.83	12.50	8.944±3.049 (2.985)	110.247±35.334 (35.016)		
	N2		6	% 18.2	23.83	15.83	19.415±4.685 (24.139)	143.912±47.344 (140.441)		
	N3		2	% 6.1	14.00	8.50	10.620±7.764 (10.620)	60.272±35.283 (60.272)		
Stage	Early Stage	I	15	% 27.3	15.71	19.08	13.234±2.240 (13.785)	204.577±35.156 (217.250)	0.210	0.043
		II	9	% 45.5						
	Advance Stag	III	9	% 27.3	20.44	11.44	15.857±3.853 (18.384)	94.720±23.120 (95.555)		
Grade	I		4	% 12.1	16.50	14.25	12.045±6.214 (7.621)	100.824±38.587 (83.326)	0.148	0.009
	II		22	% 66.7	19.05	20.41	16.565±2.387 (19.284)	221.585±35.711 (209.883)		
	III		7	% 21.2	10.86	7.86	6.815±2.521 (4.059)	69.167±32.557 (28.434)		
Histological Type	IDC		30	% 90.9	–		–			–
	ILC		3	% 9.1						

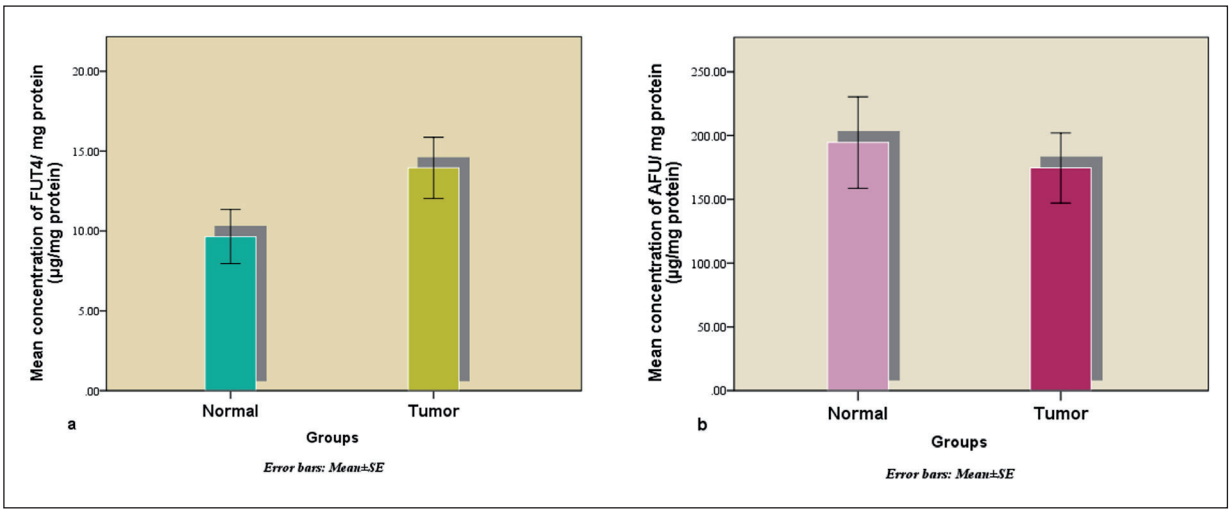

Fig. 2. Comparison of FUT4 and AFU levels between healthy and tumor tissues of patients with breast cancer. As shown in *A* and *B*, the mean level of FUT4 in tumor tissues was significantly higher than healthy ones. In addition, the AFU level was higher in the healthy group compared to the tumor group, while the difference was not significant. It should be noted that the results are expressed as mean concentration of these enzymes per mg protein.

cur in the body[6]. Although the fucosylation process is essential for normal biological function, the changes that occur at its level can contribute to the development of cancer and increase its metastatic capacity[8]. This process is dependent on the function of FUT and AFU enzymes in different tissues or cells[9]. The studies on various cancers have shown that increased fucosylation plays a role in carcinogenesis. Thus, it is expected that defucosylation improved this condition, whereas some studies have claimed that defucosylation leads to the escape from NK-cells which mediate the survival of tumors and cause more malignant features[7]. Therefore, change in the levels of these enzymes may contribute to the progression of breast cancer. Consequently, due to the lack of information in this context and sometimes inconsistencies between the results of different studies, further investigation is necessary. In the current study, we aimed to evaluate the status of AFU and FUT_4 enzymes in normal and tumor tissues of breast cancer patients who were non-diabetic and received no treatment. According to the results and as expected, the level of FUT_4 in the tumor group was significantly higher than healthy ones. These results confirm the hypothesis that changes

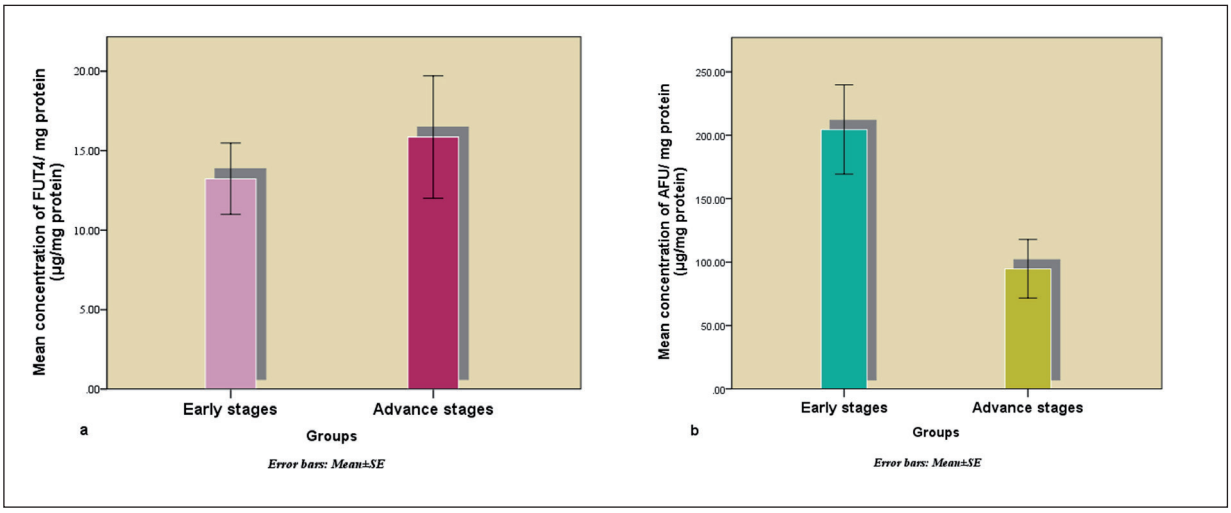

Fig. 3. Comparison of FUT4 and AFU levels between early and advanced stages of the disease. As shown in Figures *A* and *B*, there was no significant difference in the FUT4 level between early and advanced stages of the disease, while the AFU level at the early stages was significantly higher than the advanced stages. The results are expressed as the mean concentration of these enzymes per mg protein.

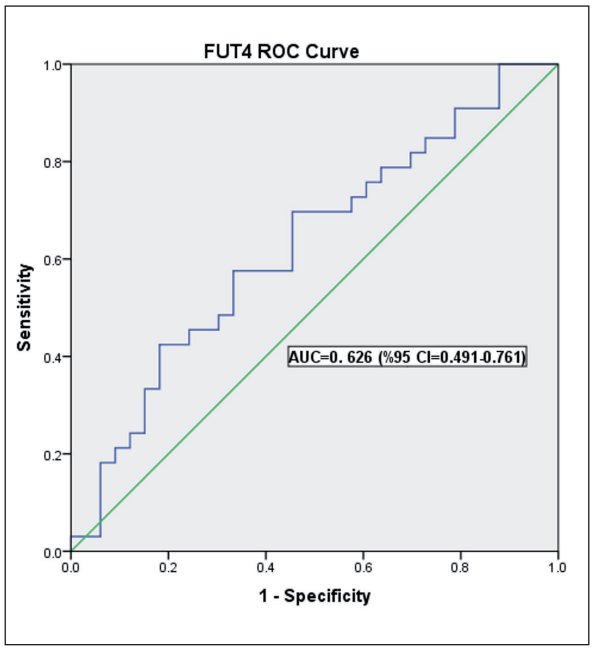

Fig. 4. Potential diagnostic accuracy of FUT4 discriminating of tumor tissues from healthy controls.

in the FUT_4 level may be involved in pathogenesis of breast cancer, and consistent with the results of two studies by Zhao et al[10] and Yang et al[13]. In this regard, Aziz et al[17] reported a higher elevation of *H. pylori* CagA, p-EGFR, FUT4, and LeY in gastric cancer compared to gastritis and gastric ulcer. They described that higher expression of FUT4 in gastric cancer indicated a close relationship between CagA and FUT4 fucosylation. Furthermore, these findings showed that the FUT_4 level was increased in the advanced stages compared to the early stages, although this difference was not significant. Thus, it seems that the tissue level of FUT_4 is not related to the stage of breast cancer. According to our knowledge, no study focused on FUT_4 status in different stages of breast cancer, but some studies investigated the role of this enzyme in tumor progression and metastasis. One of these studies was by Yan et al[5] who indicated a significant expression of FUT4 in MDA-MB compared to MCF-7 cell lines. In another study, Wu et al[18] reported that MyoD1 suppressed migration and invasion of GC cells by targeting FUT4 and inhibiting FUT4/LeY antigen expression. In addition, Zhang et al[19] reported that FUT4 is targeted by miR-125a-5p in bladder cancer, thereby affecting cell proliferation, migration, and invasion. Contrary to the findings of solid tumors, the results of a study by Dai et al[20] demonstrated that overexpression of FUT_4 is a good prognostic factor in AML, suggesting that the role of FUT_4 may be different in various disease. In the present study, there was no statistically significant relationship between the tissue level of FUT_4 and the tumor grade, tumor size, and lymph node involvement. Therefore, it seems that FUT_4 level is independent of these factors. These results were consistent with the findings by Liu et al[21] on patients with lung adenocarcinoma. Their finding revealed no statistical significance between patients with distinct FUT4 expression levels and gender, age, pT stage, pN stage, and pTNM stage. Additionally, the results of ROC analysis revealed that FUT_4 has a reasonable diagnostic accuracy for discriminating tumor tissues than healthy ones (AUC= 0.626, sensitivity= 57.6% and specificity= 66.7%). Accordingly, investigation of its pathogenesis pathways in future studies may be helpful in the early diagnosis of breast cancer. Yan et al[5] reported similar results in their study. Their findings showed that FUT_4 had higher sensitivity, specificity, and AUC compared to the CEA and CA15-3 markers and, therefore, could serve as a new indicator for breast cancer diagnosis and progression.

Moreover, we also evaluated the AFU status and observed that its level was higher in the healthy group compared to the tumor group, while the difference was not significant. Therefore, it can be considered that its level might not have significant effects on tumor induction, although other studies have shown contradictory results. One of these studies was by Cheng et al[22] who reported a high level of FUCA1 mRNA expression in breast tumor samples and early stages of disease compared to healthy groups and advanced stages, respectively. Another study was by Vajaria et al[9], which indicated significantly higher AFU activity in oral precancerous condition (OPC) and oral cancer patients compared to the controls. Besides, Junna et al[23] and Montaser et al[24] reported that AFU serum level in hepatocellular carcinoma (HCC) group was significantly higher than healthy control. Otero-Estévez et al[15] reported contradictory results *vs.* the previous issues. Their findings indicated a statistically significant decrease of FUCA1 expression in colorectal tumors compared to normal group.

In addition, a significant difference observed in AFU level between the early and advanced stages of the disease, and as expected, in the early stages, was higher compared to the advanced stages. Thus, change in its level may contribute to the progression of breast cancer. Bonin et al[16] and Cheng et al[22] agree with our results as they reported an inverse correlation between FUCA1 expression with stage and progression of breast cancer. These findings are also consistent with Otero-Estévez et al[15] who reported a gradual decrease in FUCA1 expression with the progression of colorectal cancer from earlier to advanced stages.

In the current study, no significant difference of the AFU level was observed in the different tumor sizes, while there was a statistically significant relationship between AFU level and histological tumor grades or lymph nodes involvement, such that its level in grade 2 and N0 was significantly higher than grade 3 and N1, respectively. These results were consistent with findings by Vecchio et al[25], which indicated an inverse relationship between the FUCA1 expression level and lymph node involvement in thyroid cancer. On the other hand, a study by Otero-Estevez et al[15] at colorectal cancer revealed no significant relationship between FUCA1 expression level and histological tumor grades. In another study, Xu et al[26] reported a significant association between FUCA1 overexpression and high-grade glioma. Finally, the results of the current study indicated that FUT4 and AFU may be involved in pathogenesis and progression of breast cancer. However, our findings can be affected by several variables, such as sample size, race, cancer subtypes, clinical and individual features, as well as analytical procedures or technical platforms. Therefore, in the future, we need further and larger-scale studies to validate these results and determine their potential clinical applications as diagnostic and prognostic markers for breast cancer.

CONCLUSIONS

The present study revealed that alterations in FUT4 and AFU levels may be involved in pathogenesis and progression of breast cancer. Therefore, investigation of their pathogenesis pathways in future studies may be helpful in the early diagnosis of breast cancer, prevention of its progression, as well as its therapeutic applications. Also, further and larger-scale studies are needed to confirm these findings.

Ethics approval and consent to participate:
The samples were collected with the consciously written consent of patients and after approval by the Ethics Committee of Babol Medical University (IR.MUBABOL.HRI.REC.1397.131).

Consent for publication:
The authors declare that they have consent for publication.

Availability of data and material:
The authors declare that data and material are available.

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Authors' Contributions:
DQ conceived and designed the experiments. AE performed the experiments. KH analyzed the data. AG, GhK, TU and AZ contributed to preparing the samples and writing of the manuscript.

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Limiting the Clinical State of being Beneficial of this Study:
Despite all these promising findings and suggestions, it is important to mention some of the limitations and flaws of our study. Firstly, the small sample size of this study might have led to the loss of our data 's powerful statistical analysis.

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