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Research Article

Study of lncRNA *NEAT1* Gene Expression in Ovarian Cancer

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Abstract

Long non-coding RNAs (lncRNAs) have recently emerged as effective regulatory agents in biological processes as well as in the formation of tumors. LncRNAs are important regulators of cell transformation and cancer progression. LncRNA *NEAT1* is one of the most important lncRNAs, and its deregulation has been reported in a variety of human cancers. Ovarian cancer has an inverse relationship with the number of reported pregnancies and deliveries, while it has a direct relationship with infertility. This study aimed to investigate *NEAT1* expression in ovarian cancer. A total of 140 tissue samples, including 70 ovarian tumors and 70 marginal samples, were included in the study. Total RNA was extracted using the RNXplus solution. The quality and quantity of the extracted RNAs were determined using gel electrophoresis and a NanoDrop device. The complementary DNA was synthesized by the reverse transcriptase enzyme, and quantitative reverse transcriptase PCR was used to quantify the expression of *NEAT1*. A comparison between the mean expression of *NEAT1* in ovarian tumors and marginal samples showed an increase in *NEAT1* expression in tumor tissue that was not statistically significant (P-value = 0.2). ROC curve analysis also showed that *NEAT1* expression level might not be an informative biomarker for ovarian cancer.

***Keywords*:** NEAT1, Ovarian Cancer, qRT-PCR, Biomarker

Introduction

Cancer is caused by unregulated cell division affected by environmental factors and genetic abnormalities. Recent research suggests that the extracellular matrix plays an essential role in the development of cancer (Motofei, 2021). Oncogenes, tumor suppressor genes, DNA repair genes, and programmed death genes are the main genes, and their deregulation results in cell transformation into a cancerous state (Basu, 2018). Today, one of the most prevalent and deadly diseases is cancer. According to statistics, the number of new cancer cases worldwide is anticipated to be 19.3 million, while the number of cancer fatalities is close to 10.0 million (9.9 million excluding nonmelanoma skin cancer) and adds more than 10% to the overall cost of healthcare in industrialized nations (Sung et al., 2021; Zaorsky et al., 2021).

Ovarian cancer is the seventh most prevalent malignancy among women and the eighth most common cause of cancer death. It is so lethal among female cancers that it is estimated to kill more than 140,000 people worldwide each year. (Torre et al., 2018). In the United States, approximately 19,880 new cases and 12,810 deaths of ovarian cancer were predicted in 2022 (Siegel et al., 2022). Due to its late diagnosis, it is one of the deadliest types of gynecological cancers. It is usually diagnosed in these cases when the disease has reached advanced stages and is mostly incurable (Matulonis et al., 2016). There are several types of ovarian cancer, but the most well-known type is epithelial ovarian cancer (Momenimovahed et al., 2019). Women are more likely to develop cancer, especially ovarian cancer, after menopause as a result of age-related risk factors that may raise their risk of cancer. (Koshiyama et al., 2014). A woman's lifetime risk of developing ovarian cancer is 1–1.5 percent, and the resulting death rate is approximately 50 percent. Ovarian cancer is closely related to infertility while having an inverse relationship with the number of reported pregnancies and deliveries. Ovarian cancer risk is also increased by late menopause and early puberty (Torre et al., 2018).

Non-coding RNAs are a new group of genes known in the human genome that regulate various biological processes (Ghasemi et al., 2020; Khajehdehi et al., 2021). Recently, much attention has been paid to the role of these RNAs in complex

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human diseases, including cancer (Ghasemi et al., 2021a; Khajehdehi et al., 2022; Ostovarpour et al., 2021) and neurological diseases (Khodayi-Shahrak et al., 2022; Khodayi et al., 2022). In recent years, many ncRNA genes have been identified through several different screening schemes (Khajehdehi et al., 2022; Zhang et al., 2019). They have demonstrated their capacity to be both diagnostic and therapeutic for different cancers (Fotuhi et al., 2021; Ghasemi et al., 2021a; Ghasemi et al., 2021b). Every year, increasing numbers of lncRNAs are evaluated as biomarkers for prognosis and diagnosis; a number of these have even received clinical application approval (Jarroux et al., 2017).

Nuclear Enriched Abundant Transcript 1 (*NEAT1*) is a structural component of paraspeckles that controls several genes' expression via nuclear retention (Liu et al., 2020). NEAT1 is transcribed from locus type 1 multiple endocrine neoplasms of familial tumor syndrome and is located on chromosome 11. This gene has two short (NEAT1_S) and long (NEAT1_L) isoforms that are transcribed from the same promoter and differ in their 3' end processes (West et al., 2014). It acts as a gene regulator in various cancers (Chakravarty et al., 2014; Zhen et al., 2016). Changes in expression levels of *NEAT1* have recently been reported in various human cancers, including leukemia, colorectal cancer, glioma, hepatocellular carcinoma, lung cancer, breast cancer, and prostate cancer (Dong et al., 2018). *NEAT1*'s pathogenic impact on human malignancies is attributed to the Akt and Wnt signaling pathways (Li et al., 2018; Lo et al., 2016). *NEAT1* can regulate STAT3 signaling activity via molecular processes, including microRNA sponges, transcriptional activation or inhibition, and epigenetic modifications. (ZadehRashki et al., 2022). NEAT1 also functions as a ceRNA and suppresses several tumor-suppressor miRNAs. This lncRNA is thought to be a therapeutic target and a potential biomarker in several cancer types (Ghafouri-Fard and Taheri, 2019). Cancer stem cells (CSC) generated from non-small cell lung cancer (NSCLC) had elevated *NEAT1* expression. BRCA1 may bind to the upstream region of the *NEAT1* gene to decrease *NEAT1* expression in breast tissue. *NEAT1* overexpression due to BRCA1 deficiency dramatically accelerates the formation of breast tumors (Lo et al., 2016). In contrast to most of the literature, scientists observed *NEAT1* down-regulation in invasive breast cancer, esophageal carcinomas, pheochromocytomas, and paragangliomas (Hu et al., 2018). Liu et al. examined the expression and role of *NEAT1* in the metastasis of OC cells and found that *NEAT1* was elevated in both OC tissue samples and cell lines. They also found that the knockdown of *NEAT1* prevented metastasis of OC cells via the downregulation of Rho-associated coiled-coil containing protein kinase 1 (*ROCK1*) (Liu et al., 2018). Chai et al. reported that the high expression of *NEAT1* in ovarian cancer is due to an RNA-binding protein called HUR, which increases the level of *NEAT1*. In contrast, a small non-coding RNA called miR-124-3p directly targets *NEAT1* and reduces its expression in ovarian cancer (Chai et al., 2016).

In this study, we compared expression levels of the lncRNA *NEAT1* between OC tumoral and corresponding marginal tissues and evaluated its potential as a biomarker for OC development.

Materials and Methods

Sample Collection

140 samples collected by a gynecologist, including 70 ovarian cancer and 70 marginal tissue samples, from patients referred to AL-Zahra Hospital in Tabriz. These samples were promptly frozen in liquid nitrogen, transported to the lab, and stored there until RNA extraction. The Clinical Research Ethics Committee accepted the research plan, and all individuals completed informed consent forms following AL-Zahra Hospital's standards. Clinical data were gathered both from hospital records and from interviewing patients.

RNA extraction, cDNA synthesis, and quantitative reverse transcriptase PCR

Total RNA was isolated using the RNX Plus solution (Cinnagen, Tehran, Iran) according to the manufacturer's protocol. DNase I (GeneAll, Seoul, Korea) was used to remove DNA contamination. Nanodrop (Thermo Fisher Scientific NanoDrop 2000, CA, USA) and 2% agarose gel electrophoresis (v/w) were used to evaluate the quantity and quality of RNA samples, respectively. To make cDNA, 1 µl of DNase I, 1.32 µl of DNase I buffer, equivalent to 800 ng of RNA, and water were poured into the microtube and placed in a thermocycler for 30 minutes at 37°C. 1 µl of EDTA was added and placed in the thermocycler at 65 °C for 10 minutes. 0.5 µl of Oligo dT, 0.5 µl of Random Hexamer, 0.5 µl of RT enzyme, and RT buffer were added and kept at 37 °C for 25 minutes. The reverse transcriptase enzyme was incubated for 5 minutes at 85 °C in the machine. Gene Runner software was used to design the primer. For the *NEAT1* gene, the forward primer was designed as F: CTGCCTTCTTGTGCGTTTCT,

and the reverse primer was designed as R: GACCAACTTGTACCCTCCCA. For the internal control gene, *GAPDH*, the primers were designed as F: GAGAAGTATGACAACACGCTC and R: TGAGTCCTTCCACGATAC. The real-time quantitative PCR (qPCR) assays were performed using the StepOnePlus™ Real-Time PCR System (Applied Biosystems). For both *NEAT1* and *GAPDH* genes: Master Mix SYBR Green (Amplicon Company) 5 µl, primer F 0.12 µl, primer R 0.12 µl, cDNA 4 µl (dilution 1:100), water 0.76 µl in final volume 10 µl were used. The $2^{-\Delta\Delta Ct}$ method was used to evaluate the expression level.

Statistical Analysis

The normality of the data was assessed by the Kolmogorov–Smirnov test. The Mann-Whitney test was used to evaluate differences in *NEAT1* expression between tumor and non-tumor samples. The Mann–Whitney test was also used to investigate the relationship between *NEAT1* expression and clinicopathologic characteristics. SPSS version 24, and GraphPad Prism 8 were used for statistical analysis, and P-values less than 0.05 were considered significant. The ROC curve analysis was done to assess the sensitivity and specificity of *NEAT1* as a diagnostic biomarker.

Results

Population Study

The clinicopathologic data of the patients are shown in Table 1. A total number of seventy ovarian cancer patients were enrolled in the research. Sixty-two percent (44/70) were below 55 years and 38% (26/70) were older than 55. 70% (49/70) of patients had stage I/II and the other 30% (21/70) had stage III/IV ovarian cancer. The majority of patients (54%) were nonsmokers and 46% were smokers. 70% of patients had stage I/II and the other 30% had stage III/IV ovarian cancer. Thirty-six percent (25/70) of patients had lymph metastasis and 64% (45/70) had no lymph metastasis in their tumor. Regarding invasion, 83% (58/70) of patients had invasion and the remaining had no invasion (Table 1).

Table 1. Association between lncRNA *NEAT1* expression and clinicopathological characteristics in ovarian cancer patients.

Clinical parameters	No. of cases (%)	P-value
Age		**0.16**
≤55	44 (62)	
>55	26 (38)	
TNM (Tumor stage I vs. Margins)		**0.16**
Stage I	29 (50)	
Margins	29 (50)	
TNM (Tumor stages I&II vs. margins)		**0.27**
Stages I&II	49 (50)	
Margins	49 (50)	
TNM (Tumor stages III&IV vs. margins)		**0.6**
Stage III&IV	21 (50)	
Margins	21 (50)	
TNM (Tumor stage I&II vs. III & IV)		**0.38**
Stage I&II	49 (70)	
Stage III&IV	21 (30)	
Smoking		**0.34**
No	38 (54)	
Yes	32 (46)	
Lymph		**0.78**

No	45 (64)	
Yes	25 (36)	
Invasion		**0.19**
No	12 (17)	
Yes	58 (83)	

Expression of lncRNA *NEAT1* in ovarian cancer

NEAT1 and *GAPDH* amplicons were amplified by PCR and confirmed by 2% agarose gel electrophoresis (Figure 1). The expression of *NEAT1* was quantified by qRT-PCR and compared between ovarian tumors and marginal groups. The results showed that *NEAT1* expression was high in tumor samples compared to tumor margins, but the increase was not statistically significant (p-value = 0.25) (Figure 2).

The ROC curve was also plotted by GraphPad Prism v8.0 software (Figure 3) to evaluate its potential as a biomarker for ovarian cancer. The results showed an area under the curve of 0.56, which indicates a poor potential for *NEAT1* expression level as a biomarker for ovarian cancer.

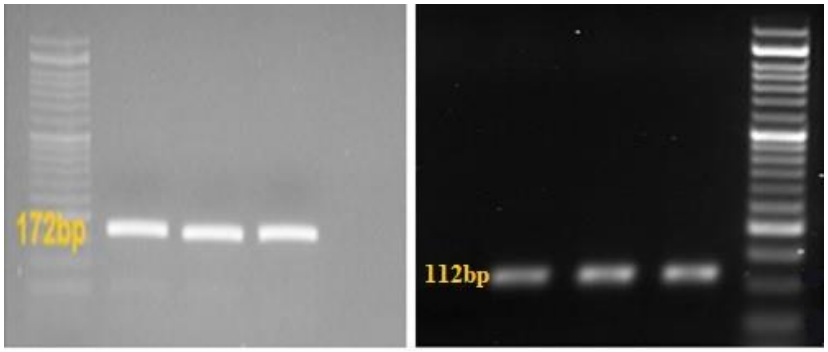

Figure 1. Gel electrophoresis of the PCR products of *GAPDH* (112 bp) and *NEAT1* (172 bp)

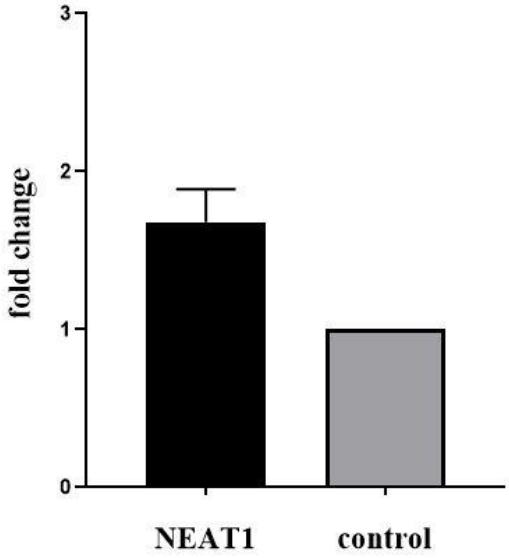

Figure 2. Fold change of *NEAT1* gene expression in tumor samples compared to the tumor margins.

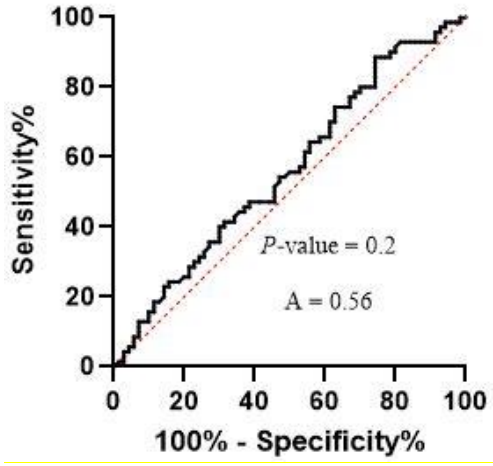

Figure 3. ROC curve analysis to evaluate the biomarker potency of *NEAT1*.

Discussion

In the present study, we examined lncRNA *NEAT1* expression in ovarian cancer. As compared to marginal tissue, the expression of lncRNA *NEAT1* was higher in ovarian tumor tissue, although the difference was not statistically significant.

One of the three forms of malignant tumors in the female reproductive system is ovarian cancer. Ovarian cancer metastases are a major cause of death, and this cancer has the highest mortality rate of any gynecological tumor. (Chen et al., 2019). Ovarian cancer patients have a poor overall survival rate despite improvements in surgery and treatment. Only 25% to 35% of women with advanced ovarian cancer survive for five years, and the prognosis is often relatively poor because of late diagnosis. More than 70% of those diagnosed with this cancer have progressed to the last stage, in which the disease has migrated past the ovaries. Understanding the molecular mechanisms involved in ovarian cancer is necessary to prevent, diagnose, and treat ovarian cancer because there is no reliable early-stage diagnostic tool, which contributes to this high death rate (Karnezis et al., 2017).

Long non-coding RNAs have recently emerged as effective regulators in biological processes as well as in the formation of tumors (Ghasemi et al., 2020; Khajehdehi et al., 2021). These are longer than 200 nucleotides and have been linked to a variety of disorders, making them prospective therapeutic targets (Nandwani et al., 2021). Multiple lncRNAs have recently been shown to be dysregulated in OC and to play key roles in tumor growth, including proliferation, apoptosis, cell cycle, migration, invasion, metastases, and pharmaceutical resistance, via a wide range of molecular processes (Fotuhi et al., 2021; Wang et al., 2019). For example, SRY-related high-mobility-group box 4 (*SOX4*), a member of the Sox family of transcription factors, showed high expression levels and caused OC cells to proliferate (Xi et al., 2017). Additionally, lncRNA *TP73-AS1* was discovered to be elevated in both OC tissues and cells by Wang, X., et al. Matrix metalloproteinase 2 (*MMP2*) and *MMP9* were primarily altered by LncRNA *TP73-AS1* to increase OC cell growth (Wang et al., 2018). Further investigations revealed that lncRNAs, including *HOXD-AS1* and *EBIC*, increased OC cell proliferation by stimulating the Wnt/beta-catenin signaling pathway (Shu et al., 2018; Xu et al., 2018; Zhang et al., 2017). Furthermore, it was shown that lncRNA *MALAT1* suppression significantly reduced the proliferation of OC cells via the PI3K-AKT pathway (Jin et al., 2017).

Recently, many studies have shown that *NEAT1* plays an important role in tumor progression (West et al., 2014). *NEAT1* expression was found to be significantly higher in prostate adenocarcinoma, stomach adenocarcinoma, liver hepatocellular carcinoma, kidney papillary cell carcinoma, and kidney clear cell carcinoma compared to normal tissues in one study of *NEAT1*. Remarkably, *NEAT1* expression was low in invasive breast carcinoma, esophageal carcinoma, and pheochromocytoma & paraganglioma compared to normal tissues. (Hu et al., 2018). Guo et al. demonstrated that *NEAT1* plays an essential role in the tumorigenesis and metastasis of hepatocellular carcinoma. (Guo et al., 2015). A study by Ma et al. showed that *NEAT1* lncRNA expression is increased in gastric adenocarcinoma. *NEAT1* may affect the progression of gastric adenocarcinoma by increasing tumor growth (Ma et al., 2016). Tankachan et al. showed that *NEAT1* is a significant biomarker with a promising future that can be used to treat breast and gynecologic cancers (Thankachan et al., 2021). Furthermore, Xu et al. reported that knocking down *NEAT1* has been shown to inhibit ovarian cancer cell proliferation, colony formation, migration, and invasion while increasing cell death (Xu et al., 2020). According to recent research by Yang et al. it was shown that NEAT1-containing paraspeckles could be produced by p53, which regulates replication stress and chemosensitivity in cancer cells (Yang et al., 2017). Knowing the functional nature of *NEAT1* in various cancers, we decided to investigate its role in ovarian cancer. This study has shown that *NEAT1* expression is increased in ovarian cancer tumor tissue compared to healthy tumor margin tissue; however, this increase was not significant.

Conclusion

The expression of *NEAT1* lncRNA in ovarian cancer tumor tissue was increased insignificantly compared to healthy tumor margin tissue, so it might not be considered a biomarker for the diagnosis and prognosis of ovarian cancer.

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Conflict of Interest
None.

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