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Research

Gene expression profiling of *lncRNA-HOTAIR* and *lncRNA-MALAT1* in esophageal cancer: uncovering links to lifestyle factors and diagnostic significance

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Abstract

Background Esophageal cancer (EC) is the sixth most common cause of cancer-related deaths globally. Genetic and environmental factors could be affected in EC's onset and development.
The potential involvement of *lncRNA-HOTAIR* and *lncRNA-MALAT1* in EC has garnered significant attention in recent studies. Our investigation aimed to examine *lncRNA-HOTAIR* and *lncRNA-MALAT1* gene expression changes in EC patients.

Materials and methods Our experimental study focused on 140 patients with malignant EC, comprising 70 paraffin-embedded tumor tissues (FFPE) blocks and 70 FFPE blocks with marginal tissue samples. The relative gene expression levels of *lncRNA-HOTAIR* and *lncRNA-MALAT1* were measured using Real-Time PCR. The data were analyzed using ANOVA and $2^{-\Delta\Delta CT}$ tests.

Results Our analysis revealed a significant increase in tumor expression compared to marginal tissues ($P < 0.05$). Besides, our research revealed a significant correlation between *lncRNA-HOTAIR* expression and hot drinks ($P = 0.019$), metastasis ($P = 0.001$), and the 5-year survival rate ($P = 0.001$). We found a significant correlation between *lncRNA-MALAT1* expression and alcohol abuse ($P = 0.039$), hot drinks ($P = 0.001$), and metastasis ($P = 0.039$).

Conclusion The findings indicate a potential carcinogenic effect of *lncRNA-HOTAIR* and *lncRNA-MALAT1* gene expression alterations in EC patients. Also, studying the lncRNA genes can help us identify biomarkers, emphasizing the significance of early diagnosis and treatment.

Keywords LncRNA · *HOTAIR* · *MALAT1* · Esophageal cancer

1 Introduction

Esophageal cancer (EC) is the eighth most frequent cancer globally and causes the sixth-highest number of cancer-related fatalities. Histologically, esophageal squamous-cell carcinomas (ESCC) and esophageal adenocarcinomas (EAC) are the two main subtypes of EC [1]. The frequency of EAC is steadily rising in Western nations. ESCC continues to hold a strong position globally [2]. Surgery is an option for treating early-stage EC patients even though most people are still diagnosed with advanced malignancy. Therefore, it appears that more research on the prognosis or early diagnosis of esophageal cancer is required [3–5]. The migration and invasion of tumor cells originating from epithelial cells is known as the epithelial-mesenchymal transition (EMT), an essential biological event. The research's preliminary focus has been

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investigating EMT-related pathways. Dysphagia that manifests at an advanced stage is frequently used to diagnose EC, which is characterized by invasive tumor growth [6, 7]. Due to the invasive disease, individuals may potentially experience tumor recurrence or re-metastasis after therapy. Currently, less than 50% of EC patients survive overall; the percentage may even be as low as 15–25 percent. Depending on the type of cancer category, the inheritance of significant genetic variables influences the susceptibility to cancer to some extent. Genome-wide association studies (GWAS) have identified numerous genetic loci associated with cancer risk within non-coding genome regions. GWA analyses revealed that alterations in the protein's amino acid sequence connected to a minor proportion (about 3.3%) of the 301 SNPs related to cancer successfully uncovered. This highly controversial finding has sparked numerous studies to examine the non-coding regions and their role in the emergence of cancer. The investigations have determined long non-coding RNAs transcribed from non-coding regions associated with cancer risk, where single nucleotide polymorphisms increase the risk of developing cancer. Investigations have revealed that lncRNA plays an important function in regulating EMT. One specific type of lncRNA transcribed from the HOX locus at q13.13.12 is referred to as *LncRNA-HOTAIR* [2, 3, 7–9]. Several deconstructions have studied the overexpression of *lncRNA-HOTAIR* in ESCC, suggesting its association with the progressive TNM stage and weak biological differentiation [10]. Investigators uncovered that *lncRNA-HOTAIR* can control the polycomb repressive complex 2 (PRC2) by methylating the H3K27 of the *WIF-1* promoter region. This inhibition leads to decreased *WIF-1* expression and production, raising TCF/LEF and reduced beta-catenin levels, finally triggering the Wnt/beta-catenin signaling pathway [11]. This mechanism causes the target gene to become overexpressed, leading to raised invasion and distance of tumor cells, which *LncRNA-HOTAIR* may also support EMT. *LncRNA-HOTAIR* depletion leads to increased E-cadherin expression and reduced vitamin and MMP-9 levels in colorectal cancer cells. Thus, *LncRNA-HOTAIR* is offered as a conceivable new molecular controller for EMT [12]. Recent research on carcinogenesis has shown two forms of LncRNA that are essential players in the process: *MALAT1* and *NEAT2*. Overexpression of *lncRNA-MALAT1*, which acts as a critical prognostic factor, has been noticed in some malignancies, including lung carcinoma and gallbladder cancer [13, 14].

Reduced hybridization in EAC, NSCL-1, and ESCC patients has disclosed that *lncRNA-MALAT1*, an 8.7 kb nucleus-specific lncRNA, is a predictive characteristic of metastasis [15]. The downregulation of *lncRNA-MALAT1* inhibits the apoptosis pathway, resulting in the upregulation of caspase-3 and -8 and the downregulation of *Bcl-2* and *Bcl-xl* [16]. This lncRNA upregulates in different solid tumors, such as breast, pancreatic, colon, prostate, and liver malignancies. Moreover, differentiable gene expression links it to tumor recurrence and metastasis [17]. The present study aimed to measure the differences in gene expression levels of *lncRNA-HOTAIR* and *lncRNA-MALAT1* in EC patients and emphasize the importance of understanding these lncRNAs in cancer.

2 Materials and methods

2.1 Tissue samples

This experimental study, which analyzed 140 individuals diagnosed with malignant EC at Tabriz International Hospital from 2012 to 2019, has constructed results that significantly improve our understanding of this disease. The investigation involved 70 patients in the two groups. The first group received tumor tissue samples, while the second group received marginal tissue samples. Pathologists and gastroenterologists diagnosed the paraffin samples from the pathology archive used for data collection. The international medical oncology community considers all patients included based on the clinical criteria for the diagnosis of EC. According to the International Union Against Cancer (UICC), patients considered using the tumor-node-metastasis staging system (TNM). Pathologists considered individuals with distinctly malignant EC stages I through IV suitable for inclusion in the study. Patients undergoing chemotherapy or having formerly surgery were excluded from the study. We received signed reported permission and questionnaires from each patient, and the Ahar Branch of Islamic Azad University validated our investigation.

2.2 Sample processing

The Nucleo Spin total RNA FFPE kit (Germany) was used to extract RNA from tumor and non-tumor tissues. RNA extraction was performed during DNase treatment. Before cDNA synthesis, the extracted RNA's quality and quantity were evaluated by UV spectrophotometry at 260/280 nm and 2% Agarose gel electrophoresis (using the NanoDrop TM ND-1,000, NanoDrop Technology, Wilmington, DE, USA). All extracted RNA samples were stored at -80 °C until analysis.

The RevertAid™ First Strand cDNA Synthesis Kit from Thermo Fisher, Inc., in the United States, was used for reverse transcription (RT).

2.3 REAL-TIME PCR

We achieved quantitative real-time polymerase chain reaction (qRT-PCR) employing specific primers to investigate the gene expression differences of *lncRNA-HOTAIR* and *lncRNA-MALAT1* in cancerous versus non-cancerous tissues. For *lncRNA-HOTAIR* [18], forward: 5′-CAGTGGGGAACTCTGACTCG-3′ and reverse: 5′-GTGCCTGGTGCTCTCTTACC-3′; for *lncRNA-MALAT1*; for *GAPDH* as the housekeeping gene, forward: 5′-GTAAGACCCCTGGACCACCA-3′ and Reverse: 5′-CAAGGGGTCTACATG GCAACT-3′ [19, 20]. To prepare the reaction mixture for qRT-PCR, use the following components: 1 µl of each primer (at a concentration of 10 pmol), 16 µl of SYBR Green Real-Time PCR Master Mix (produced by Takara, Japan), and 2 µl of cDNA. The qRT-PCR examination was achieved employing the ABI7500 System from Applied Biosystems in California, USA. qRT-PCR was used to analyze the *lncRNA-HOTAIR* and *lncRNA-MALAT1* genes. A total of 45 amplification cycles were completed. Each cycle contained an initial denaturation phase at 94 °C for 3 min, followed by three stages: denaturation at 94 °C for 30 s, annealing at 59 °C for 30 s, and extension at 72 °C for 40 s.

2.4 Statistical analysis

We employed the Pearson correlation test to evaluate the levels of *lncRNA-HOTAIR* and *lncRNA-MALAT1* gene expression changes in tumor and margin tissues. Furthermore, we used a chi-square test to investigate the relationship between different clinical characteristics and the expression levels of the lncRNAs *MALAT1* and *HOTAIR*. A two-tailed p-value of less than 0.05 was regarded as showing a significant difference in statistical significance.

3 Results

3.1 LncRNA-HOTAIR gene expression levels in EC patients

Our study, conceived to evaluate the *lncRNA-HOTAIR* gene expression levels in EC patients and identify its potential as a powerful prognostic marker, promises to pave the way for a more precise and effective approach to managing EC, instilling hope and optimism in the field. Our analysis, which included 70 confirmed cases of EC, was comprehensive and inclusive, with a balanced distribution of 33 (47.14%) male and 37 (52.85%) female patients, ensuring a robust and representative sample for our study. Each subject in our investigation, carefully selected to ensure the accuracy and reliability of our findings, underwent surgical intervention as part of their treatment. The cohort, with an age range of 33 to 70 and a mean age of 61.11 ± 3.25, was meticulously chosen, instilling confidence in the robustness of our study. In the current investigation, the expression levels of the *lncRNA-HOTAIR* gene in tumor and margin tissues were assessed using real-time PCR. The expression of *lncRNA-HOTAIR* was significantly higher in tumor samples compared to non-cancerous tissues ($P < 0.05$) (Fig. 1).

We categorized subjects into two groups based on the median expression levels of *lncRNA-HOTAIR*: high-expression (median amount ≥ 1) and low-expression (median amount < 1). In addition to assessing expression levels, we investigated the relationship between various clinicopathological variables and *lncRNA-HOTAIR* expression in EC patients. We identified significant associations between *lncRNA-HOTAIR* expression and factors such as hot drink use, metastasis, and the 5-year survival rate ($P = 0.019$, $P = 0.001$, $P = 0.001$, respectively). None of the following factors showed significant relationships with *lncRNA-HOTAIR* expression: socioeconomic status ($P = 0.739$), smoking status ($P = 0.309$), alcohol abuse ($P = 0.301$), or phases ($P = 0.907$) (see Table 1). The discoveries mentioned provide critical insights into the potential role of *lncRNA-HOTAIR* as a prognostic marker and its association with specific clinical attributes in patients with EC.

3.2 LncRNA- MALAT1 gene expression levels in EC subjects

Compared to the non-cancerous margin samples, tumor samples exhibited a significant increase in the expression levels of the *lncRNA-MALAT1* gene ($p < 0.001$) (Fig. 2).We divided the participants into two groups based on *lncRNA-MALAT1* expression levels: a high-expression group (median amount ≥ 1) and a low-expression group (median amount < 1). This classification facilitated a thorough comparison and analysis of gene expression levels among the

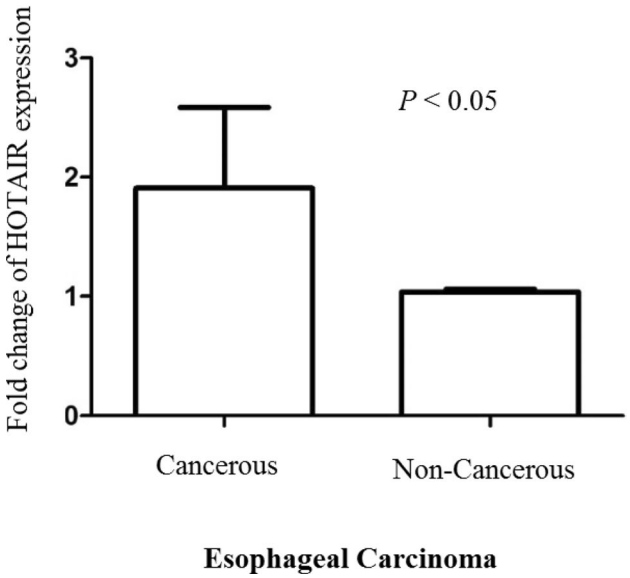

Fig. 1 The fold change of *LncRNA-HOTAIR* gene in cancerous versus non-cancerous tissues ($P < 0.05$)

Table 1 The relationship between *lncRNA-HOTAIR* and *lncRNA-MALAT1* expression and patient's demographic and clinical features

Variables	HOTAIR			MALAT1		
	Low	High	P-value	Low	High	P-value
Stage of disease			0.907			0.304
Stages I, II	23.0	14.0		20.0	17.0	
Stages III, IV	22.0	16.0		12.0	26.0	
Smoking status			0.309			0.642
High	19.0	9.0		23.0	5.0	
Low	27.0	20.0		32.0	15.0	
Alcohol abuse			0.301			0.039
High	12.0	9.0		6.0	15.0	
Low	36.0	18.0		32.0	22.0	
Hot drinks			0.019			0.001
Yes	19.0	27.0		12.0	34.0	
No	12.0	17.0		14.0	15.0	
Socioeconomic status			0.739			0.552
Good	41.0	16.0		32.0	25.0	
Poor	8.0	10.0		6.0	12.0	
Metastasis			0.001			0.001
Non-distant metastasis	12.0	18.0		16.0	14.0	
Distant metastasis	19.0	26.0		13.0	32.0	
5-year survival rate			0.001			0.193
Positive	14.0	20.0		16.0	18.0	
Negative	11.0	30.0		20.0	21.0	

research population. We found significant correlations between changes in *lncRNA-MALAT1* gene expression and factors like hot drink intake, metastasis, and alcohol addiction ($P = 0.001$).

However, the expression of the *lncRNA-MALAT1* gene and other tumor characteristics did not show a significant correlation ($P > 0.05$) (Table 1). The results indicate the potential role of *lncRNA-MALAT1* in tumor differentiation and its correlation with specific demographic factors. These results emphasize the potential role of *lncRNA-MALAT1* in tumor differentiation and its correlation with specific demographic factors. Only weak correlations existed between the *lncRNA-HOTAIR* expression changes and specific clinical traits.

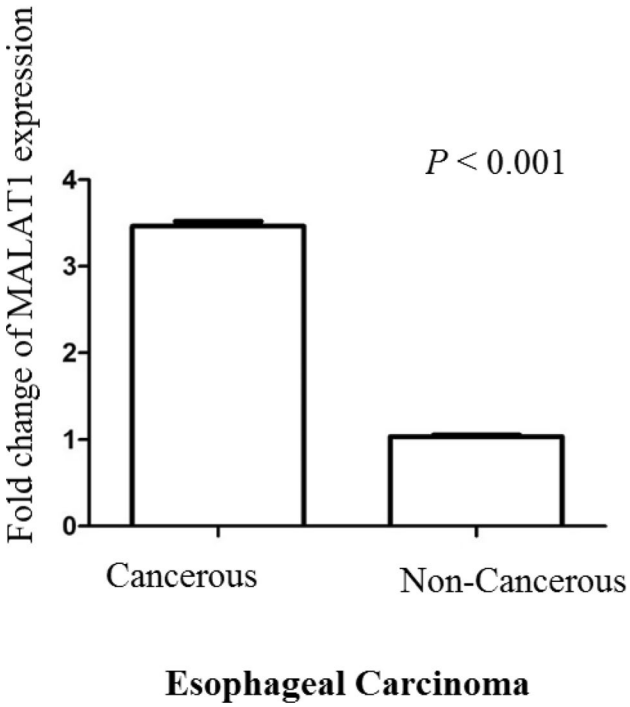

Fig. 2 The fold change of *LncRNA-MALAT1* gene in cancerous versus non-cancerous tissues ($P < 0.001$)

4 Discussion

Epigenetic regulation by the *lncRNA-HOTAIR* is a crucial mechanism in cancer control. Research shows that chromatin-modifying complexes, including LSD1, PRC2, and COREST/REST, regulate the transcription of human HOX genes throughout the genome. *LncRNA-HOTAIR* serves as a guiding framework, steering these sets to their specific target genes. Unlike the LSD1/COREST combination, which removes methyl groups from H3K4, the PRC2 complex adds methyl groups to H3K27, deactivating *lncRNA-HOTAIR* target genes. Research suggests that *lncRNA-HOTAIR* functions as a negative regulator of osteogenic genes such as BMP2 and ALPL, indicating its role as an inhibitor of osteogenesis. Furthermore, *lncRNA-HOTAIR* is involved in cellular senescence through its interactions with E3 ubiquitin ligases. Additionally, it plays a crucial role in cell proliferation by modulating the expression of proteins and kinases associated with the cell cycle. Investigations have shown that *LncRNA-HOTAIR* is significantly expressed in BC; measuring its levels is crucial for predicting patient prognosis and evaluating the risk of tumor spread in early-stage BC. Different types of cancers are associated with the function of *lncRNA-HOTAIR*. It is overexpressed not only in primary pancreatic cancer but also in sarcoma, hepatocellular carcinoma, CRC, laryngeal squamous cell carcinoma, and nasopharyngeal cancer [21–26].The study examined the expression of *lncRNA-HOTAIR* in EC patients, finding that tumor tissues exhibited significantly higher gene expression levels than marginal tissues. Studies have shown that *lncRNA-HOTAIR* is a competitive endogenous RNA in the lncRNA-mRNA network, which is critical for EC. *LncRNA-HOTAIR* levels have significantly increased in ESCC cells. This increase in *lncRNA-HOTAIR* led to the upregulation of sponging miR-1 and CCND1, which supports the proliferation of ESCCs. These findings highlight the significance of understanding the role of *lncRNA-HOTAIR* in EC and its potential as a therapeutic target for treatment [27]. Xu et al. indicate that *lncRNA-HOTAIR* may enhance the expression of snail2 by functioning as a sponge for miR-148a, thereby stimulating EMT. According to reports, homeobox C8 (HOXC8) is up-regulated in several cancer types and has a role in the creation of tumors [28]. Han et al. revealed that *lncRNA-HOTAIR* can attach to miR-204 as an endogenous RNA candidate to regulate HOXC8. The involvement of CC motif chemokine ligand 18 (CCL18) in tumor metastasis and progression is substantial [29]. Additionally, the determinations displayed that the miR-130a-5p and zinc finger E-box binding homeobox 1 axis, in which CCL18 promoted *lncRNA-HOTAIR*, accelerated the malignant growth of ESCC. Of particular note, tumors demonstrate a heightened hexokinase 2 (HK2) expression, a significant contributor to aerobic glycolysis. Ma et al. (2017) discovered that *lncRNA-HOTAIR* sponging of miR-125/miR-143 led to an increased expression of HK2, a crucial factor in the development of ESCC. Understanding the intricate mechanisms of *lncRNA-HOTAIR* influence on HK2 is critical in our battle against ESCC (29). *LncRNA-MALAT1* plays

a significant role in controlling the phosphorylation and distribution of serine-arginine processing factors in nuclear speckles, thereby influencing intermittent processing.The upregulation of *lncRNA-MALAT1* in many tumor tissues enhances the proliferation and migration [30]. Research indicates that the expression of *lncRNA-MALAT1* increases significantly in certain types of prostate, bladder, and kidney cancers. It enhances cancer cells' growth, survival, and movement and is notably overexpressed in urothelial carcinoma. This lncRNA activates the Wnt signaling pathway, facilitating the transition from an epithelial to a mesenchymal state in laboratory conditions. In renal cell carcinoma, *lncRNA-MALAT1* interacts with TFEB, a regulatory transcription factor involved in developmental pathways [31]. The complete TFEB coding sequence remains intact during the integration process. Research has uncovered a significant mechanism in cancer development. The fusion *lncRNA-MALAT1* with malignant cells leads to increased cancer development and higher TFEB protein levels. Furthermore, *lncRNA-MALAT1* directly enhances gene expression, a critical factor in cancer progression [32]. Two lncRNAs, *MALAT1* and *TUG1*, promote PRC2 interaction with repressed and activated growth-regulating genes. TUG1 expression significantly increases in the later stages of the illness and is elevated in genitourinary cancers [33]. Overexpression of *lncRNA-MALAT1* has been identified in multiple tumor types, including gastric, endometrial, colon, lung, bladder, breast, cervical, and colorectal cancers [34–39]. The results of this analysis were in line with the findings of earlier investigations. Wang et al. [40] investigated the impact of *lncRNA-MALAT1* expression on patients with EC. The research indicated that *lncRNA-MALAT1* plays a crucial role in cancer development and tumor growth, serving as both a molecular marker and a target for cancer therapy. McCabe et al. noted that *lncRNA-MALAT1* plays a critical role in facilitating the EMT induced by TGF-B. Inhibiting *lncRNA-MALAT1* may serve as a potential approach for monitoring bladder cancer progression [41]. Hu et al. [42] demonstrated that *lncRNA-MALAT1* functions as an oncogene by modulating the ATM-CHK2 pathway, thereby regulating the development of ESCC tumors. Additionally, the expression of *lncRNA-MALAT1* in tumor tissues may be critical for its regulation. During the progression of ESCC, gene amplification occurs within the tumor tissues. In individuals diagnosed with ESCC, the expression of *lncRNA-MALAT1* is significantly higher in cancerous tissues than in the adjacent normal tissues. Suppressing the expression of *lncRNA-MALAT1* in cancer cell lines leads to several significant effects: it reduces cell growth, increases programmed cell death, decreases cell movement and invasion, lowers the formation of cell clusters, and halts the cell cycle at the G2/M phase [43]. Research indicates that lowering *lncRNA-MALAT1* levels halts the G2/M phase of the cell cycle by activating the checkpoint kinase 2/ataxia-telangiectasia mutated pathway through phosphorylation. Furthermore, it increases the number of cells that undergo apoptosis. *LncRNA-MALAT1* is associated with the sensitivity of ESCC cells to chemotherapy and radiation. The suppression of *lncRNA-MALAT1* leads to the enhancement of the sensitivity of ESCC cells to chemotherapy and radiation. Cyclin-dependent kinase subunit 1 (Cks1) expression was elevated in ESCCs. Upregulation of Cks1 was associated with increased radiation resistance [43]. Li et al. discovered that Cks1 and *lncRNA-MALAT1* expression levels decreased in ESCC mice xenografts and cells after irradiation. The upregulation of *lncRNA-MALAT1* also prevented irradiation-induced decreases in cell viability, increases in apoptosis, and reductions in Cks1 levels. The authors conclude that *lncRNA-MALAT1* is a positive regulator of radioresistance in ESCC, potentially enhancing the effectiveness of radiotherapy in this condition [44]. The suppression of *lncRNA-MALAT1* has revealed a decrease in cell migration and invasion, a sensation related to increased miR-1-3p expression, and a decrease in the activity of CORO1C/TPM3. The findings exhibited that *lncRNA-MALAT1* is directly associated with the seed sequence of miR-1-3p, resulting in the downregulation of miR-1-3p levels. This interchange improves the activity of the CORO1C/TPM3 signaling pathway and promotes the expression of *lncRNA-MALAT1*, suggesting an interdependent connection between *lncRNA-MALAT1* and miR-1-3p in the context of EC invasion and metastasis. In addition, research has shown that miR-101 and miR-217 significantly affect the expression of *lncRNA-MALAT1*, which in turn is crucial for regulating cell invasion and metastasis. This influence is mediated through their effects on downstream genes, including MIA2, HNF4G, ROBO1, CCT4, and CTHRC1 [45]. Several significant obstacles are evident when examining the constraints related to research on *lncRNA-MALAT1* and *lncRNA-HOTAIR*, particularly regarding their involvement in esophageal cancer and other areas. The challenges originate from the fundamental characteristics of lncRNAs, the techniques employed to study these molecules, and the real-world implications of the findings. One significant limitation of this research is its small sample size, which may affect the reliability of the findings. Engaging a larger number of medical centers and obtaining a broader spectrum of patient samples is essential to enhancing the diagnostic relevance of *lncRNA-MALAT1* and *lncRNA-HOTAIR* as clinical biomarkers for EC. This approach will facilitate a more thorough assessment of treatment efficacy and progress. A notable limitation highlighted in the research on *lncRNA-MALAT1* and *lncRNA-HOTAIR* is the relatively small number of studies conducted across different geographical locations. This scarcity may impact the ability to generalize the findings to a broader range of ethnic populations. The restricted geographical focus of this research may limit the extent to which the findings could be applied to other regions.

Findings indicate a need for more extensive and diverse study samples to verify the predictive potential of *lncRNA-MALAT1* and *lncRNA-HOTAIR* across various cancer types, including EC.

5 Conclusion

The research indicates a significant association between esophageal cancer and the overexpression of *lncRNA-HOTAIR* and *lncRNA-MALAT1*. These lncRNAs appear significantly elevated in tumor tissues and cancer cells, suggesting their potential role in the disease's progression. The findings suggest that their gene expression may serve as a potential genetic marker for esophageal cancer. Furthermore, future research should explore the impact of other cancer-associated lncRNAs on the development and progression of esophageal cancer. Additionally, further research is necessary to understand the methylation processes affecting the promoters of *lncRNA-HOTAIR* and *lncRNA-MALAT1*.

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Author contributions Saeid Ghorbian: Conceived and designed the experiments; Analyzed and interpreted the data. Vahid Ghorbani: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The work was approved by the Ahar Branch Islamic Azad University (MSc.ID: 950187436), and informed written consent was filled out by all participants. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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