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UPREGULATION OF LONG NON-CODING RNA HOTAIR IN ORAL SQUAMOUS CELL CARCINOMA, ORAL POTENTIALLY MALIGNANT LESIONS VERSUS CONTROL PATIENTS: A CASE-CONTROL STUDY

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is one of the most common tumors in the head and neck area. Recent research suggests that the increased expression of the long non-coding RNA (lncRNA) HOTAIR correlates with the progression of many cancer types.

The aim of this study: The objective of this research was to ascertain if levels of long non-coding RNA HOTAIR in saliva are advantageous and correspond among the oral squamous cell cancer (OSCC) group, the oral potentially malignant lesions (OPMLs) group, and the control group.

Materials & Methods: A total of 45 participants (n=15) were evenly allocated into three distinct groups. Group A, diagnosed with OSCC; Group B, diagnosed with OPMLs; and Group C, the control group. Saliva samples were collected from participants through unstimulated spitting and subsequently preserved in sterile vials. The extraction of LncRNA HOTAIR from saliva was conducted, followed by preparation for genetic analysis utilizing Reverse Transcription (RT) and real-time Quantitative PCR (qPCR).

Results: No statistically significant variations were found between the groups concerning gender; nevertheless, highly statistically significant disparities were noted between the median ages of the control group and those of the premalignant and OSCC groups. Concerning HOTAIR expression, a significantly significant disparity was seen between the OSCC and control groups, however no significant difference was noted between the OPMLs and control groups.

Conclusions: The expression of HOTAIR is linked to OSCC and may serve as a crucial target in its evolution. Nonetheless, HOTAIR is not implicated in the tumor progression of OPMLs.

KEYWORD: HOTAIR, oral squamous cell carcinoma, oral potentially malignant lesions, long noncoding RNAs.

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INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) represents 600,000 new cases annually throughout the globe (Sung et al., 2021). This malignancy manifests in several anatomical sites, such as the oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, palatine tonsils, and lingual tonsils (Marur & Forastiere, 2008). Oral squamous cell carcinoma (OSCC) constitutes around 3% of all malignancies and exceeds 274,000 newly diagnosed cancer cases globally each year (de Camargo Cancela et al., 2010). Consequently, an early diagnosis strategy for OSCC is essential to enhance long-term patient survival.

Timely detection of HNSCC is essential for therapy, emphasizing the molecular pathways involved in cancer progression. Long non-coding RNAs (lncRNAs) have a significant role in the genesis of malignancy (Guglas et al., 2018). Multiple genetic and epigenetic alterations facilitate tumorigenesis and progression. Epigenetic modifications, including long noncoding RNAs (lncRNAs), serve as significant biomarkers for gastrointestinal malignancies due to their association with genomic and epigenomic alterations (Bhan et al., 2017; Grady et al., 2021).

LncRNAs, non-coding RNAs with over 200 nucleotides, participate in several biological processes and are recognized as cancer-related entities owing to their interactions with DNA, RNA, or proteins, rendering them promising for malignancy diagnosis and prognosis (Qi et al., 2016).

HOX transcript antisense RNA (HOTAIR), a 2.2-kb-long non-coding RNA found on chromosome 12q13.13, transcribed from the homeobox C gene (HOXC) locus, has been recognized as a regulator of cancer *(Cai et al., 2014; Qu et al., 2019)*. HOTAIR is a well-known long noncoding RNA that was first characterized in breast cancer *(Gupta, Shah, Wang, Kim, Horlings, Wong, Tsai, Hung, Argani, Rinn, Wang, Brzoska, Kong, Li, West, van de Vijver, et al., 2010)*. Numerous studies have been published on HOTAIR, a gene associated with lung cancer, and its abnormal expression has been linked to various cancer sites *(Loewen et al., 2014)*, cervical cancer *(Zhou et al., 2020)*, breast cancer *(Pawłowska et al., 2017)*, and gastrointestinal cancers *(Geng et al., 2011; Kogo et al., 2011)* and glioblastoma *(Angelopoulou et al., 2020)*.

In oral cancer, HOTAIR facilitates the inhibition of cell proliferation and the enhancement of apoptosis (Liu et al., 2015) while also promoting the invasion and metastasis of OSCC via metastasis-associated gene 2 (MTA2) (Tao et al., 2020). Numerous studies indicate that HOTAIR inhibition results in G0/G1 cell cycle arrest, thereby impeding tumor cell growth (Firoz et al., 2022). The systematic review and meta-analysis by G. Yang et al. (2022a) indicated that HOTAIR may function as a superior predictive biomarker and predictor of clinicopathologic characteristics in HNSCC (G. Yang et al., 2022b).

The upregulation of the long non-coding RNA HOTAIR has been consistently associated with the advancement and unfavorable prognosis of many squamous cell carcinomas, including OSCC, esophageal carcinoma, and laryngeal carcinoma. In OSCC, the overexpression of HOTAIR correlates with metastasis, advanced disease stage, and reduced survival (Y. Wu et al., 2015a). This indicates that HOTAIR may function as a prospective diagnostic marker for various malignancies, including OSCC, and as a target for therapeutic intervention.

Oral cancer is a malignancy for which salivary evaluation demonstrates significant advantages owing to its direct contact with cancer cells. Saliva has emerged as the preferred medium for the screening and identification of biomarkers due to the presence of exfoliated cancer cells in the mouth cavity. Numerous salivary indicators for oral cancer have been documented together with their clinical

relevance (Zimmermann et al., 2007). Among all cancers, oral squamous cell carcinoma has the most significant advantages from salivary analysis. The primary rationale for saliva's diagnostic importance is because malignant cells are discharged directly into the oral cavity, making it the preferred medium for identifying biomarkers for OSCC (J.-Y. Wu et al., 2010). Saliva is inherently wired to react to certain stimuli. Consequently, cancer growth and metastasis demonstrated variations in the expression of proteins, genes, RNAs, and many inflammatory cytokines. Ultimately, these expressions are beneficial for the surveillance of individuals at risk for cancer (Yakob et al., 2014).

This study was aimed at determining whether long non-coding RNA HOTAIR levels in saliva are beneficial and correlate among the OSCC group, OPMLs group versus the control group. The null hypothesis was that there is a statistically significant correlation among long non-coding RNA HOTAIR levels in saliva in the patients with OSCC and patients with OPMLs.

PATIENTS AND METHODS

This research had 45 people evenly divided into three groups: Group A comprises 15 patients diagnosed with oral squamous cell carcinoma (OSCC); group B includes 15 patients diagnosed with oral potentially malignant lesions (OPMLs); and group C serves as the control group, consisting of 15 healthy individuals. All patients in groups (A) and (B) were classified as OSCC or OPMLs based on pathological analysis of surgical specimens. In patients with OSCC, tumor features such as size, nodal metastasis, and distant metastases were documented using the TNM classification system. The 15 participants in group (C) were presumably healthy controls, with no previous diagnoses of malignant tumors or other medical disorders, including diabetes mellitus or hypertension. All participants were chosen from the outpatient clinic of the Oral Medicine and Oral Diagnosis department at the Faculty of Oral and Dental Medicine, Cairo University.

The sample size was calculated using Epicalc program version 1.02 assuming a power of 80 % and alpha=0.05; Where the attrition rate was adjusted to be 20%. The sample size is based on the specificity of HOTAIR was 95% (Xie et al., 2016).

This study protocol and the template informed consent forms used for this study were reviewed and approved by the ethical committee, Faculty of Oral and Dental Medicine, Cairo university, with respect to scientific content and compliance with applicable research and human subjects' regulations.

All subjects had comprehensive history taking, including demographic information, medical history, and prior surgical interventions. All chosen participants must fulfill the following criteria: they must be medically free from any systemic disorders; they must not have had chemotherapy or radiation treatment; all participants must sign the informed consent form and must be readily contactable. All at-risk populations, including incarcerated individuals and participants with mental disabilities, were excluded from this research.

This study also excluded pregnant and lactating women. Both genders were involved and all participants ranged in age from 20 to 70.

Biochemical assessment of salivary samples:

Saliva samples were obtained from subjects using unstimulated spitting and stored in sterile vials. LncRNA HOTAIR was extracted from saliva using the MiRNeasy extraction kit (Qiagen, Valencia, CA, USA). Chloroform, ethanol, and buffer RWT were added to the column. The mixture was centrifuged at 8000 x g for 15 seconds, and then 50 uL of RNase-free water was added to the column. The extracted microRNA was stored at -80˚C until use. The process involved several steps to ensure accurate results.

Reverse transcription (RT) and real-time Quantitative PCR (qPCR):

Qiagen's miScript II RT kit was used for reverse transcription of LncRNA HOTAIR extracted from saliva. Real-time qPCR was performed using a MiScript SYBR Green PCR kit and miScript primer assay LncRNA HOTAIR. Melting curve analyses were performed to validate the expected PCR product. GAPDH* was used as an endogenous control. Expression levels of HOTAIR** was calculated relative to the control samples (used as the calibrator sample) using the formula $2^{-\Delta\Delta Ct}$ and were expressed as a fold change.

Statistical data analysis:

The collected data was reviewed, processed, tabulated, and entered into a computer using the Statistical Package for the Social Sciences (SPSS 15.0 for Windows; SPSS Inc, Chicago, IL, 2001). Data was given, and appropriate analysis was conducted based on the kind of data acquired for each parameter.

Values were expressed as mean ± standard deviation (SD), median, minimum and maximum values (range) for numerical data, and frequency and % for categorical data. The normality of distribution parameters was first assessed using the One-Sample Kolmogorov-Smirnov test, followed by the use of the One-Way ANOVA test to evaluate the statistical significance of differences among more than two group averages, assuming normal distribution. Unidirectional Analysis of Variance Post Hoc Tests were used when disparities among the means were identified. Post hoc range tests and pairwise multiple comparisons may identify which means are significantly different. Range tests determine homogenous groups of means that are statistically indistinguishable from one another. The pairwise multiple comparisons test evaluates the differences between each pair of means, producing a matrix where asterisks indicate substantially different group means at an alpha level of 0.05. The Chi-Square test was used to analyze the association between two qualitative variables, whereas Fisher's precise Chi-Square test is utilized when a contingency table, not derived from missing rows or columns in a bigger table, has a cell with an anticipated frequency of less than 5. The significance level was designated as statistically non-significant (NS) for p-values >0.05, statistically significant (S) for p-values ≤0.05, and highly significant (HS) for p-values ≤0.01.

RESULTS

Demographic data:

The study enrolled a total of 45 participants. Approximately 19 (42.2%) were males and 26 (57.8%) were females. The detailed gender distribution among the study groups is presented in Table (1). In summary, there were no statistically significant differences between groups regarding gender.

TABLE (1) Comparison between groups regards gender

Gender	*Control* (n=15)	OPMLs (n=15)	OSCC (n=15)	Total (n=45)	X^2	P Value	Sig.
Male	**4(26.7%)**	**9(60%)**	**6(40%)**	**19(42.2%)**	**3.5**	**0.177**	**NS**
Female	**11(73.3%)**	**6(40%)**	**9(60%)**	**26(57.8%)**			

* GAPDH, F: 5'-TCAAGGCTGAGAACGGGAAG-3', R: 5'-TGGACTCCACGACGTACTCA-3'.
** HOTAIR, F: 5'-CAGTGGGGAACTCTGACTCG-3', R: 5'-GTGCCTGGTGCTCTCTTACC-3'

The median age for the control group was 34 years (range: 32–51 years), for the pre-malignant group was 53 years (range: 34–70 years), and for the OSCC group was 52 years (range: 38–65 years). Highly statistically significant differences were observed between the median ages of the control group and those of the premalignant and OSCC groups. No statistically significant differences were observed between the ages of OSCC and premalignant groups. The median age of the control group was lower than that of the premalignant and OSCC groups by 19 and 18 years, respectively. Table (2) presents a comparison of age among the study groups.

Salivary expression of HOTAIR:

This study observed elevated levels of HOTAIR expression in the OSCC group. The mean HOTAIR expression was 13.3 ± 14.0 for the OSCC group, 6.8 ± 1.6 for the premalignant group, and 1.0 ± 0.1 for the control group.

The mean salivary HOTAIR expression in the OSCC group surpassed that of the control group by 12.3, indicating a highly statistically significant difference between the two groups. The mean values of HOTAIR in OSCC were also 6.5 greater than those in the premalignant group, indicating a statistically significant difference between the two groups. No statistically significant difference was seen in HOTAIR expression between the control group and the premalignant group, since HOTAIR expression levels for the premalignant group were higher than those of the control group by 5.8. Table (3) presents the mean and median values of HOTAIR expression for the three groups.

TABLE (2) Comparison between group regards age

	Group	N	Mean	SD	Median	Range		F	P Value	Sig.
						Min.	Max.			
Age	Control [a]	15	38.5	7.8	34.0	32.0	51.0	10.8	<0.001	HS
	OPMLs [b,c]	15	51.9	12.0	53.0	34.0	70.0			
	OSCC [c,b]	15	52.5	7.5	52.0	38.0	65.0			

TABLE (3) Comparison between group regards HOTAIR expression

	Group	N	Mean	SD	Median	Range		F	P Value	Sig.
						Min.	Max.			
HOTAIR	Control [a,c]	15	1.0	0.1	1.0	.8	1.2	8.6	0.001	HS
	OPMLs [c,a]	15	6.8	1.6	6.5	4.9	9.5			
	OSCC [b]	15	13.3	14.0	12.9	1.2	43.1			

DISCUSSION

Head and neck squamous cell carcinoma impacts around 600,000 persons globally each year, with significant risk factors including tobacco use, alcohol intake, and HPV infection (Bray et al., 2018). Notwithstanding advancements in surgical methods, radiation, and immunotherapy, many cases are identified at advanced stages, leading to poor prognoses (Marur & Forastiere, 2016).

Early detection of oral squamous cell carcinoma (OSCC) significantly decreases the necessity for aggressive treatments, improves treatment outcomes, and increases patient survival rates (Marur & Forastiere, 2016). Current research is elucidating the molecular mechanisms underlying the development of HNSCC, highlighting alterations in pathways including EGFR, PI3K/AKT, NOTCH, and TP53. These pathways play a crucial role in the regulation of tumor progression, immune resistance, and metastasis. The identification of biomarkers within these systems facilitates early detection and allows for more precise, targeted treatment strategies (Leemans et al., 2018).

HOTAIR was first identified for its role in the progression of breast cancer (Gupta et al., 2010). Subsequent studies indicate that HOTAIR is linked to various cancers, including head and neck squamous cell carcinoma, where it contributes to metastasis and adverse medical consequences (Troiano et al., 2017).

This study selected saliva for examination due to its emerging role as a diagnostic fluid for oral squamous cell carcinoma (OSCC). Cancer cells are directly shed into the oral cavity, rendering saliva an optimal source for biomarker detection (Cristaldi et al., 2019). Saliva collection offers a diverse range of biomarkers for various diseases and is characterized by its noninvasive nature and convenience. Additionally, its ease of transportation and storage contributes to its cost-effectiveness and overall efficiency (Kaczor-Urbanowicz et al., 2017).

Historically, OSCC has exhibited a higher prevalence in men, primarily attributable to increased tobacco and alcohol consumption among this demographic. Recent research indicates that the gender gap is narrowing, particularly in contexts where women increasingly participate in risk behaviors and face heightened occupational exposure to carcinogens such as ultraviolet radiation and human papillomavirus (HPV) (Singh et al., 2016; Lee et al., 2021; Z. Yang et al., 2023). No statistically significant gender differences were identified between the groups in our demographic analysis. The findings correspond with a study from Northeastern Iran, which indicated a nearly equivalent male-to-female ratio (0.99:1) in OSCC cases (Saghravanian et al., 2025). This phenomenon may be attributed to the increase in tobacco and alcohol consumption among women in recent decades (White, 2020).

In contrast, our results indicated a statistically significant difference in the median ages between the control group and the premalignant and OSCC groups. This is consistent with research conducted in Iran, which found a mean age of 56.9 years among OSCC patients, predominantly affecting individuals over 60 years old (Andisheh-Tadbir et al., 2008). Recent trends indicate a concerning rise in OSCC cases among younger populations. A study in the Netherlands indicated a significant annual increase of 2.4% in OSCC incidence among individuals aged 20–34 years from 1989 to 2010 (Al-Jamaei et al., 2022). The rising incidence of OSCC among younger populations is often associated with lifestyle factors, notably tobacco and alcohol consumption (Abdulla et al., 2018).

Our study has identified statistically significant elevated levels of HOTAIR expression in the OSCC cohort compared to the control group. This aligns with the findings of Tao et al. (2020), who reported that HOTAIR is markedly overexpressed in OSCC tissues in relation to adjacent normal mucosa.

Furthermore, its heightened expression correlates with advanced tumor stages, poor histological differentiation, and metastasis to regional lymph nodes.

Furthermore, Wu et al. (2015) investigated the correlation between HOTAIR expression and clinicopathological features in OSCC patients, underscoring HOTAIR's crucial involvement in tumor growth. Their results indicated that HOTAIR was significantly overexpressed in both OSCC tissue samples and cell lines relative to normal oral mucosa and human oral keratinocytes. The upregulation may be ascribed to recent studies demonstrating that HOTAIR enhances OSCC development by boosting epithelial-mesenchymal transition (EMT), a key mechanism in cancer metastasis. It does this by enlisting the polycomb repressive complex 2 (PRC2), which catalyzes histone changes, namely H3K27me3, in the E-cadherin promoter, thereby inhibiting E-cadherin production. This inhibition augments cellular motility and invasiveness (Song et al., 2018; Tao et al., 2020b).

Furthermore, HOTAIR has been shown to influence cancer stem cell (CSC) traits in OSCC. Its elevated expression enhances CSC-like properties, such as greater self-renewal capacity and tumor-forming ability. In contrast, silencing HOTAIR reduces these characteristics and leads to decreased tumor growth in xenograft models *(Lu et al., 2017)*. In addition, reduced HOTAIR expression in OSCC cancer stem cells (OCSCs) led to the suppression of EMT-related traits. These findings suggest that HOTAIR regulates OCSC behavior by modulating EMT markers, highlighting its potential as a promising therapeutic target for OSCC treatment *(Lu et al., 2017)*.

OPMLs are often present at the initial stages of malignant oral mucosal disease development. These lesions have a high likelihood of transforming into invasive OSCC. In clinical practice, OPMLs usually appear visibly abnormal and are commonly linked with conditions like oral leukoplakia (OLK), oral lichen planus (OLP), oral submucous fibrosis (OSF), or other potentially malignant disorders *(Malik et al., 2016)*. OPMLs develop through early stages involving the accumulation of genetic and phenotypic alterations, including modifications in non-coding RNAs, within the normal oral mucosa *(Yap et al., 2019)*.

To date, there have been no studies detailing the expression patterns of HOTAIR in OPMLs. In this research, we examined HOTAIR expression in the premalignant group to explore its potential role in the tumorigenesis of OPMLs. However, our statistical analysis showed no significant difference in HOTAIR expression levels between the control and premalignant groups, suggesting that HOTAIR may not play a role in the tumorigenesis of OPMLs. Additional research on the biological function of HOTAIR is needed to validate this lack of association.

CONCLUSION

The expression of HOTAIR in saliva serves as a reliable and non-invasive diagnostic indicator for OSCC, complementing surgical biopsy and histopathologic examination; however, it lacks reliability for diagnosing OPMLs.

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