ORIGINAL ARTICLE

Immunohistochemical Evaluation of p53 and Ki-67 Expression in Oral Leukoplakia and Oral Squamous Cell Carcinoma

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ABSTRACT

Background

Oral leukoplakia (OL) is one of the most common oral potentially malignant disorders, with a reported malignant transformation rate of 0.13-17.5%. Oral squamous cell carcinoma (OSCC) accounts for over 90% of oral malignancies. Molecular biomarkers such as p53 and Ki-67 play crucial roles in identifying lesions at higher risk of malignant transformation.

Methods

A cross-sectional study was conducted on 75 formalin-fixed paraffin-embedded tissue blocks (25 OL, 25 OSCC, and 25 NOM). Immunohistochemistry was performed using standard protocols for p53 and Ki-67. The percentage of positively stained cells was calculated and analyzed statistically. Results: p53 expression was significantly higher in OSCC (68.4 ± 12.3%) compared to OL (42.7 ± 15.6%) and NOM (8.3 ± 4.2%) ($p < 0.001$). Ki-67 expression followed a similar pattern with highest expression in OSCC (54.2 ± 11.8%), intermediate in OL (28.9 ± 10.4%), and lowest in NOM (5.7 ± 3.1%) ($p < 0.001$). A positive correlation was observed between p53 and Ki-67 expression in both OL ($r = 0.58$, $p = 0.002$) and OSCC ($r = 0.63$, $p < 0.001$). Dysplastic OL showed significantly higher expression of both markers compared to non-dysplastic OL ($p < 0.05$).

Conclusion

The progressive increase in p53 and Ki-67 expression from NOM to OL to OSCC suggests their role in oral carcinogenesis. These markers may help identify OL lesions at higher risk of malignant transformation, potentially improving patient management and outcomes.

Keywords

Oral leukoplakia, Oral squamous cell carcinoma, p53, Ki-67, immunohistochemistry, biomarkers

INTRODUCTION

Oral cancer remains a significant global health concern, ranking as the sixth most common cancer worldwide [1]. Oral squamous cell carcinoma (OSCC) represents over 90% of all oral malignancies, with a 5-year survival rate of approximately 50-60% despite advances in treatment modalities [2]. The development of OSCC is often preceded by oral potentially malignant disorders (OPMDs), with oral leukoplakia (OL) being one of the most prevalent [3].

OL is clinically defined as a white plaque of questionable risk having excluded other known diseases or disorders that carry no increased risk for cancer [4]. The malignant transformation rate of OL varies widely from 0.13% to 17.5% depending on factors such as tobacco use, alcohol consumption, presence of epithelial dysplasia, and clinical characteristics [5]. Histopathological assessment of dysplasia remains the gold standard for determining malignant potential, though it is subject to inter-observer variability and may not always predict transformation accurately [6].

Molecular biomarkers have emerged as valuable tools to complement histopathological assessment in identifying lesions at higher risk of malignant transformation. Among these, p53 and Ki-67 have gained significant attention in oral carcinogenesis research [7].

The p53 tumor suppressor gene, located on chromosome 17p13, plays a crucial role in

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cell cycle regulation, DNA repair, and apoptosis [8]. Mutations in the TP53 gene are among the most common genetic alterations in human cancers, including OSCC [9]. Immunohistochemical detection of p53 protein accumulation often reflects TP53 gene mutations, though wild-type p53 accumulation can also occur due to other mechanisms [10].

Ki-67 is a nuclear protein expressed during all active phases of the cell cycle (G1, S, G2, and M) but absent in resting cells (G0) [11]. As a proliferation marker, Ki-67 provides valuable information about the growth fraction of cells and has been correlated with tumor aggressiveness and prognosis in various malignancies, including OSCC [12].

Recent studies have demonstrated the utility of p53 and Ki-67 as biomarkers in oral carcinogenesis. A systematic review by Liu et al. [13] reported that p53 overexpression was associated with a 3.5-fold increased risk of malignant transformation in OPMDs. Similarly, increased Ki-67 expression has been linked to higher grades of dysplasia and malignant transformation potential [14].

Despite these findings, there remains a research gap regarding the comparative expression patterns of these markers in OL with varying degrees of dysplasia and OSCC. Additionally, the relationship between p53 and Ki-67 expression in oral carcinogenesis warrants further investigation. Understanding these patterns could improve risk stratification and management of patients with OL.

This study aims to evaluate and compare the immunohistochemical expression of p53 and Ki-67 in OL, OSCC, and normal oral mucosa (NOM) to determine their potential as biomarkers for malignant transformation and to explore the relationship between these markers in oral carcinogenesis.

MATERIALS AND METHODS

Study Design and Sample Collection

This cross-sectional study was conducted using archived formalin-fixed paraffin-embedded (FFPE) tissue blocks from the Department of Oral Pathology and Microbiology between January 2018 and December 2022. Ethical approval was obtained from the Institutional Review Board (IRB/2023/OPM/045).

A total of 75 FFPE tissue blocks were included in the study, divided into three groups:

1. Oral leukoplakia (OL) (n = 25)
2. Oral squamous cell carcinoma (OSCC) (n = 25)
3. Normal oral mucosa (NOM) (n = 25)

The NOM samples were obtained from healthy individuals undergoing third molar extraction or other minor oral surgical procedures, with informed consent.

Inclusion and Exclusion Criteria

Inclusion Criteria:

a) OL: Clinically diagnosed white patches that were histopathologically confirmed as OL with or without dysplasia

b) OSCC: Histopathologically confirmed cases of well-differentiated OSCC

c) NOM: Histologically normal mucosal tissue without inflammation or other pathological changes

d) Adequate tissue material for immunohistochemical processing

Exclusion Criteria:

a) Patients who had received prior radiotherapy or chemotherapy

b) Tissue blocks with inadequate material or poor preservation

c) Recurrent lesions

d) Lesions with other concurrent oral potentially malignant disorders

Tissue Processing and Immunohistochemistry

Sections of 4 µm thickness were cut from FFPE blocks and mounted on positively charged glass slides. The sections were deparaffinized in xylene and rehydrated through graded alcohol to distilled water.

For antigen retrieval, the sections were heated in citrate buffer (pH 6.0) for p53 and Tris-EDTA buffer (pH 9.0) for Ki-67 in a pressure cooker for 10 minutes. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 minutes.

The sections were then incubated with primary antibodies:

- Mouse monoclonal anti-p53 antibody (Clone DO-7, Dako, Denmark) at 1:100 dilution for 60 minutes at room temperature
- Mouse monoclonal anti-Ki-67 antibody (Clone

MIB-1, Dako, Denmark) at 1:150 dilution for 60 minutes at room temperature

Following primary antibody incubation, the sections were washed in phosphate-buffered saline and incubated with a horseradish peroxidase-conjugated secondary antibody (EnVision+ System, Dako, Denmark) for 30 minutes. The reaction was visualized using 3,3'-diaminobenzidine (DAB) as the chromogen, and sections were counterstained with Harris hematoxylin.

Positive controls included known p53-positive breast carcinoma tissue and tonsil tissue for Ki-67. Negative controls were prepared by omitting the primary antibody.

Evaluation Criteria

Immunohistochemical staining was evaluated independently by two experienced oral pathologists who were blinded to the clinical data. In cases of disagreement, a consensus was reached after joint review.

For p53 expression, nuclear staining was considered positive. The percentage of positively stained tumor cells was calculated in 5 randomly selected high-power fields (HPFs) (400x magnification). Cases were categorized as:

- Negative: <10% positive cells
- Low expression: 10-30% positive cells
- Moderate expression: 31-60% positive cells
- High expression: >60% positive cells

For Ki-67 expression, nuclear staining was considered positive. The Ki-67 labeling index (LI) was calculated as the percentage of positively stained cells among 1000 cells counted in 5 randomly selected HPFs (400x magnification). Cases were categorized as:

- Low proliferation: LI < 25%
- Moderate proliferation: LI 25-50%
- High proliferation: LI > 50%

Statistical Analysis

Statistical analysis was performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables.

The normality of data distribution was assessed using the Shapiro-Wilk test. For normally distributed data, one-way ANOVA followed by Tukey's post-hoc test was used for comparisons among the three groups. For non-normally distributed data, the Kruskal-Wallis test followed by Dunn's post-hoc test was employed.

The chi-square test was used to compare categorical variables between groups. Pearson's correlation coefficient was used to assess the relationship between p53 and Ki-67 expression. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic Data

The study included 75 tissue samples distributed equally among OL, OSCC, and NOM groups. Table 1 presents the demographic characteristics of the study population. The mean age was highest in the OSCC group (56.8 ± 10.2 years), followed by OL (49.3 ± 11.7 years) and NOM (35.6 ± 12.4 years). There was a male predominance in both OL (68%) and OSCC (76%) groups, while the NOM group had an equal gender distribution. The most common site for OL was buccal mucosa (44%), while tongue was the most common site for OSCC (52%).

Table 1: *Demographic characteristics of the study population*

Parameter	OL (n=25)	OSCC (n=25)	NOM (n=25)	p-value
Age (years, mean ± SD)	49.3 ± 11.7	56.8 ± 10.2	35.6 ± 12.4	<0.001*
Gender (n, %)				0.042**
Male	17 (68%)	19 (76%)	13 (52%)	
Female	8 (32%)	6 (24%)	12 (48%)	
Site (n, %)				<0.001**
Buccal mucosa	11 (44%)	6 (24%)	10 (40%)	
Tongue	6 (24%)	13 (52%)	8 (32%)	
Gingiva	5 (20%)	3 (12%)	4 (16%)	
Palate	2 (8%)	2 (8%)	2 (8%)	
Floor of mouth	1 (4%)	1 (4%)	1 (4%)	

*p-value from ANOVA; **p-value from chi-square test*

OL: Oral leukoplakia; OSCC: Oral squamous cell carcinoma; NOM: Normal oral mucosa

p53 Expression

p53 expression was predominantly nuclear in all positive cases. The mean percentage of p53-positive cells was significantly higher in OSCC (68.4 ± 12.3%) compared to OL (42.7 ± 15.6%) and NOM (8.3 ± 4.2%) ($p < 0.001$). The difference between OL and NOM was also statistically significant ($p < 0.001$).

When OL cases were categorized based on the presence of dysplasia, dysplastic OL (n=14) showed significantly higher p53 expression (51.8 ± 13.4%) compared to non-dysplastic OL (n=11) (30.9 ± 11.2%) ($p = 0.002$).

Table 2 shows the distribution of p53 expression categories among the study groups. High p53 expression (>60% positive cells) was observed in 68% of OSCC cases, 28% of OL cases, and none of the NOM cases. The difference in p53 expression categories among the three groups was statistically significant ($p < 0.001$).

Table 2: *Distribution of p53 expression categories among study groups*

p53 Expression	OL (n=25)	OSCC (n=25)	NOM (n=25)	p-value
Negative (<10%)	2 (8%)	0 (0%)	21 (84%)	<0.001*
Low (10-30%)	6 (24%)	2 (8%)	4 (16%)	
Moderate (31-60%)	10 (40%)	6 (24%)	0 (0%)	
High (>60%)	7 (28%)	17 (68%)	0 (0%)	

*p-value from chi-square test

OL: Oral leukoplakia; OSCC: Oral squamous cell carcinoma; NOM: Normal oral mucosa

Ki-67 Expression

Ki-67 expression was also predominantly nuclear in all positive cases. The mean Ki-67 labeling index was significantly higher in OSCC (54.2 ± 11.8%) compared to OL (28.9 ± 10.4%) and NOM (5.7 ± 3.1%) ($p < 0.001$). The difference between OL and NOM was also statistically significant ($p < 0.001$).

When OL cases were categorized based on the presence of dysplasia, dysplastic OL (n=14) showed significantly higher Ki-67 expression (35.2 ± 9.8%) compared to non-dysplastic OL (n=11) (20.6 ± 7.3%) ($p = 0.001$).

Table 3 shows the distribution of Ki-67 expression categories among the study groups. High Ki-67 proliferation (LI > 50%) was observed in 52% of OSCC cases, 12% of OL cases, and none of the NOM cases. The difference in Ki-67 expression categories among the three groups was statistically significant ($p < 0.001$).

Table 3: *Distribution of Ki-67 expression categories among study groups*

Ki-67 Expression	OL (n=25)	OSCC (n=25)	NOM (n=25)	p-value
Low proliferation (<25%)	13 (52%)	2 (8%)	25 (100%)	<0.001*
Moderate proliferation (25-50%)	9 (36%)	10 (40%)	0 (0%)	
High proliferation (>50%)	3 (12%)	13 (52%)	0 (0%)	

*p-value from chi-square test

OL: Oral leukoplakia; OSCC: Oral squamous cell carcinoma; NOM: Normal oral mucosa

Correlation between p53 and Ki-67 Expression

A positive correlation was observed between p53 and Ki-67 expression in both OL ($r = 0.58$, $p = 0.002$) and OSCC ($r = 0.63$, $p < 0.001$) groups. This correlation was stronger in OSCC compared to OL.

DISCUSSION

The present study evaluated and compared the immunohistochemical expression of p53 and Ki-67 in OL, OSCC, and NOM to determine their potential as biomarkers for malignant transformation. Our findings demonstrate a progressive increase in both p53 and Ki-67 expression from NOM to OL to OSCC, suggesting their involvement in oral carcinogenesis.

In our study, p53 expression was significantly higher in OSCC (68.4 ± 12.3%) compared to OL (42.7 ± 15.6%) and NOM (8.3 ± 4.2%). This progressive increase in p53 expression aligns with the multistep theory of oral carcinogenesis, where genetic alterations accumulate as normal epithelium transforms into potentially malignant disorders and subsequently into carcinoma [15].

The mean p53 expression in OSCC observed in our study is consistent with previous reports. A meta-analysis by González-Moles et al. [16] reported p53 positivity in approximately 55% of OSCC cases, with variations attributed to methodological differences,

antibody clones, and scoring systems.

The significantly higher p53 expression in dysplastic OL (51.8 ± 13.4%) compared to non-dysplastic OL (30.9 ± 11.2%) in our study suggests that p53 accumulation may be associated with the progression of dysplasia. This finding is supported by a systematic review by Napier et al. [17], which reported that p53 positivity was significantly associated with the presence and grade of epithelial dysplasia in OPMDs.

The accumulation of p53 protein in oral lesions can result from various mechanisms. While TP53 gene mutations are the most common cause, other factors such as viral proteins (particularly HPV E6), interaction with MDM2, and cellular stress can also lead to p53 accumulation [18]. In the context of oral carcinogenesis, tobacco-derived carcinogens can cause specific TP53 mutations, leading to dysfunctional p53 protein that accumulates in the nucleus [19].

Our study demonstrated a significant increase in Ki-67 expression from NOM (5.7 ± 3.1%) to OL (28.9 ± 10.4%) to OSCC (54.2 ± 11.8%). This progressive increase in cellular proliferation reflects the increasing growth fraction of cells during oral carcinogenesis.

The mean Ki-67 labeling index in OSCC observed in our study is comparable to previous reports. A systematic review by Pichardo-Lowden et al. [20] reported Ki-67 labeling indices ranging from 30% to 80% in OSCC, with higher values associated with poor prognosis and increased risk of recurrence.

The significantly higher Ki-67 expression in dysplastic OL (35.2 ± 9.8%) compared to non-dysplastic OL (20.6 ± 7.3%) in our study suggests that cellular proliferation increases with the progression of dysplasia. This finding is consistent with a study by Kujan et al. [21], which reported that Ki-67 expression correlated with the grade of epithelial dysplasia in OPMDs.

The increased Ki-67 expression in oral lesions reflects alterations in cell cycle regulation. During oral carcinogenesis, various molecular events disrupt the normal balance between cell proliferation and apoptosis, leading to uncontrolled cellular proliferation [22]. Ki-67, being expressed throughout the active phases of the cell cycle, serves as an effective marker to quantify this increased proliferation.

Correlation between p53 and Ki-67 Expression

Our study demonstrated a positive correlation between p53 and Ki-67 expression in both OL ($r = 0.58$, $p = 0.002$) and OSCC ($r = 0.63$, $p < 0.001$) groups. This correlation suggests that p53 alterations may contribute to increased cellular proliferation during oral carcinogenesis.

The relationship between p53 and Ki-67 in oral carcinogenesis is complex. Wild-type p53 normally regulates the cell cycle by inducing p21, which inhibits cyclin-dependent kinases and arrests the cell cycle [23]. When p53 is mutated or functionally inactivated, this regulatory mechanism is disrupted, potentially leading to uncontrolled cellular proliferation as reflected by increased Ki-67 expression.

Our findings are consistent with previous studies that have reported a positive correlation between p53 and Ki-67 in oral lesions. A study by Alves et al. [24] found a significant positive correlation between p53 and Ki-67 expression in OSCC, suggesting that p53 alterations may contribute to increased proliferative activity.

Clinical Implications

The progressive increase in p53 and Ki-67 expression from NOM to OL to OSCC observed in our study has several clinical implications:

1. Risk Stratification: The significantly higher expression of both markers in dysplastic OL compared to non-dysplastic OL suggests their potential utility in identifying lesions at higher risk of malignant transformation. This could help clinicians prioritize surveillance and intervention strategies.
2. Complementary Diagnostic Tool: Immunohistochemical evaluation of p53 and Ki-67 could complement histopathological assessment, particularly in cases with equivocal dysplasia grading. This may help address the issue of inter-observer variability in dysplasia assessment.
3. Prognostic Indicator: The higher expression of both markers in OSCC suggests their potential as prognostic indicators. Previous studies have linked high p53 and Ki-67 expression with poor prognosis, increased risk of recurrence, and reduced survival in OSCC [25, 26].
4. Therapeutic Target: The involvement of p53 in oral carcinogenesis makes it a potential therapeutic target. Recent advances in gene therapy and molecular targeted therapy against p53-altered cancers offer promising avenues for future OSCC treatment [27].

CONCLUSION

The present study demonstrated a progressive increase in p53 and Ki-67 expression from normal oral mucosa to oral leukoplakia to oral squamous cell carcinoma. Both markers were significantly higher in dysplastic compared to non-dysplastic oral leukoplakia, suggesting their potential utility in identifying lesions at higher risk of malignant transformation. The positive correlation between p53 and Ki-67 expression indicates that p53 alterations may contribute to increased cellular proliferation during oral carcinogenesis.

These findings support the role of p53 and Ki-67 as valuable biomarkers in oral carcinogenesis and suggest their potential application in risk stratification of oral potentially malignant disorders. However, further longitudinal studies with larger sample sizes are needed to validate these findings and determine the clinical utility of these markers in predicting malignant transformation and patient outcomes.

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