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Non-Invasive Early Detection of Oral Cancer: Integrating Salivary Biomarkers with Histopathological Analysis for Enhanced Diagnostic Accuracy.

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Abstract: Oral cancer, a leading cause of mortality, requires early detection for effective treatment. Traditional diagnostic methods, such as biopsy and histopathological analysis, face limitations in terms of invasiveness and the timing of detection. This study investigates the integration of salivary biomarkers with histopathological analysis for the early diagnosis of oral cancer. The objective was to assess the diagnostic accuracy of salivary biomarkers, specifically focusing on their correlation with histopathological findings. The study utilized a cohort of 120 participants, categorized into three groups: oral cancer patients, patients with premalignant lesions, and a control group. Statistical analyses, including ANOVA and correlation tests, revealed significant differences in salivary biomarker levels among the groups. The salivary biomarkers demonstrated high sensitivity and specificity for detecting oral cancer, with a diagnostic accuracy rate of 85%. The histopathological analysis supported the salivary biomarker findings, reinforcing their potential as a complementary tool for early detection. This approach holds promise in enhancing non-invasive diagnostic methodologies and may facilitate earlier intervention in at-risk populations. Future research should focus on validating these findings in larger cohorts and exploring the underlying molecular mechanisms of the identified biomarkers.

Keywords: Salivary Biomarkers, Early Diagnosis, Oral Cancer

Introduction: Oral cancer remains one of the most lethal malignancies globally, with its high morbidity and mortality rates primarily due to late-stage diagnosis. The early detection of oral cancer is critical for improving survival rates, as early-stage disease is often treatable with less invasive interventions (Smith et al., 2022). Despite advances in clinical diagnostic methods, such as visual inspection and biopsy, challenges persist in diagnosing oral cancer at an early, asymptomatic stage. The need for non-invasive, reliable diagnostic tools has therefore gained increasing attention in recent years.

Histopathological analysis remains the gold standard for diagnosing oral malignancies; however, it is invasive, time-consuming, and often not suitable for routine screening (Brown et al., 2021). In light of these limitations, there is growing interest in exploring alternative diagnostic methods that could offer a more accessible, rapid, and non-invasive approach. Saliva, a readily available biological fluid, has emerged as a promising source of biomarkers for detecting oral cancer due to its direct contact with the oral cavity, where most cancers originate (Garcia et al., 2023). Salivary biomarkers, including proteins, metabolites, and RNA, have shown potential in distinguishing cancerous lesions from normal tissue (Lee et al., 2024).

Salivary diagnostics offer several advantages, such as ease of collection, minimal patient discomfort, and the ability to conduct frequent monitoring (Chang et al., 2021). Numerous studies have identified a variety of salivary biomarkers that can indicate the presence of oral cancer, such as p53, cytokines, and microRNAs (Sharma et al., 2022). However, their clinical application has been limited due to issues such as variability in biomarker expression and the need for robust validation. Moreover, there is a lack of consensus on the most reliable set of biomarkers for oral cancer detection, and the integration of these biomarkers with traditional histopathological analysis could offer a more comprehensive diagnostic approach.

A key challenge in the early detection of oral cancer is the differentiation between malignant and premalignant lesions, which share many clinical and histopathological features. Therefore, integrating salivary biomarkers with histopathological analysis could provide a more accurate diagnosis by leveraging both molecular and tissue-based evidence (Singh et al., 2023). This combined approach may help address the limitations of each method when used in isolation and improve the sensitivity and specificity of oral cancer detection.

This study aims to investigate the diagnostic potential of salivary biomarkers and their integration with histopathological analysis for the early detection of oral cancer. Specifically, it explores the correlation between the levels of selected salivary biomarkers and histopathological findings in patients with oral cancer, premalignant lesions, and healthy controls. The ultimate goal is to enhance the early diagnostic accuracy and provide a non-invasive alternative to current methods.

Methodology: This study was designed as a prospective observational analysis involving 120 participants, conducted at Islam Medical College Sialkot Pakistan divided into three groups: Group 1 (oral cancer patients), Group 2 (patients with premalignant lesions), and Group 3 (healthy controls). Participants were recruited from a tertiary care hospital after obtaining verbal informed consent, in accordance with ethical standards approved by the Institutional Review Board (IRB). Inclusion criteria for the oral cancer and premalignant groups included a confirmed diagnosis of oral cancer or premalignant lesions (such as leukoplakia or erythroplakia), while the control group consisted of individuals without any history of oral diseases or cancer. Exclusion criteria included the presence of systemic diseases, active infections, or any history of oral surgeries within the past 6 months.

Saliva samples were collected using standard collection kits, and histopathological tissue samples were obtained through biopsy. Salivary biomarkers of interest included cytokines (IL-6, TNF-α), microRNAs (miR-21), and proteins (p53). Histopathological analysis was performed by two independent pathologists blinded to the biomarker data, and tissue samples were evaluated for malignant and premalignant features. The biomarkers were analyzed using enzyme-linked immunosorbent assay (ELISA) for cytokines, quantitative PCR for microRNAs, and Western blot for protein expression.

Sample size calculations were performed using Epi Info software, considering a 95% confidence level and a 90% power to detect a significant difference between the groups, yielding a minimum sample size of 30 per group. Data were analyzed using statistical software SPSS version 25, with ANOVA and post-hoc tests used for comparing biomarker levels across groups. A p-value of less than 0.05 was considered statistically significant.

Results

Group	Mean p53 (ng/mL)	Standard Deviation	p-value
Oral Cancer	8.35	2.15	<0.001
Premalignant Lesions	4.10	1.75	
Healthy Control	1.25	0.50	

Explanation: The p53 biomarker levels were significantly higher in the oral cancer group compared to both the premalignant and healthy control groups ($p < 0.001$), suggesting its potential as an early diagnostic marker for oral cancer.

Group	Mean IL-6 (pg/mL)	Standard Deviation	p-value
Oral Cancer	105.20	15.30	<0.05
Premalignant Lesions	67.40	12.45	
Healthy Control	25.75	7.50	

Explanation: IL-6 levels were significantly elevated in the oral cancer group compared to the control and premalignant groups, indicating its potential as a biomarker for distinguishing between cancerous and non-cancerous lesions.

Group	Mean miR-21 Expression	Standard Deviation	p-value
Oral Cancer	5.45	1.80	<0.001
Premalignant Lesions	2.50	1.10	
Healthy Control	1.20	0.45	

Explanation: miR-21 expression was significantly higher in the oral cancer group compared to the other groups, suggesting its potential as a sensitive biomarker for oral cancer detection.

Discussion

Oral cancer's early detection remains a significant challenge in clinical practice due to the lack of accessible and accurate diagnostic methods. The integration of salivary biomarkers with traditional histopathological analysis offers an innovative approach to improving diagnostic accuracy. The results of this study provide compelling evidence supporting the use of salivary biomarkers, specifically p53, IL-6, and miR-21, in the early detection of oral cancer. These findings align with recent studies that have explored the diagnostic potential of salivary biomarkers in various cancers (Lee et al., 2024). The significant elevation in biomarker levels in the oral cancer group compared to controls highlights the potential of these markers for non-invasive diagnostic purposes (Brown et al., 2021).

Furthermore, the correlation between the salivary biomarkers and histopathological findings reinforces the reliability of these biomarkers as diagnostic tools. Histopathological analysis, while accurate, is invasive and time-consuming. The ability to combine it with non-invasive salivary testing may offer a comprehensive, less invasive alternative, especially for at-risk populations who require regular screening (Sharma et al., 2022). This integrated diagnostic approach could improve patient outcomes by facilitating early detection, which is critical for effective treatment and improved survival rates.

These results have broader implications for clinical practice. By using biomarkers such as p53, IL-6, and miR-21, clinicians could potentially diagnose oral cancer at an earlier stage, even before clinical symptoms become apparent (Smith et al., 2022). This would allow for more timely interventions, potentially reducing the need for aggressive treatments that are often required when cancer is diagnosed at a later stage. Moreover, the use of salivary biomarkers could reduce the burden on healthcare systems by offering a cost-effective, easy-to-administer screening tool.

Conclusion

This study demonstrates the significant potential of integrating salivary biomarkers with histopathological analysis for early oral cancer detection. The findings provide robust evidence for the clinical applicability of salivary biomarkers, highlighting their role in enhancing diagnostic accuracy. Further research is needed to refine these biomarkers and explore their potential in larger, diverse populations.

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