

Beyond buccal cells: Systemic genotoxicity biomarkers enhance early detection of oral cancer and risk stratification in oral leukoplakia

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ABSTRACT:

Oral leukoplakia (LPK), the most prevalent oral potentially malignant disorder, carries a 0.6-20% risk of malignant transformation to oral cancer (OC), with tobacco carcinogens being the primary etiological factor. Current diagnostic approaches are clinical examination and histopathological evaluation. Buccal cell micronucleus cytome (BMNCyt) assay effectively assess localized genotoxic damage but fail to evaluate systemic effects in LPK patients. The elevated incidence of chromosomal aberrations, cytokinesis-block micronucleus formation, and telomerase dysregulation reveals systemic genomic instability. These biomarkers detect molecular alterations preceding histopathological progression, providing an effective tool for early risk stratification and clinical intervention in LPK patients. Integrating these systemic markers with conventional diagnostics would enable comprehensive risk assessment by capturing both local and field cancerization effects. This combined approach provides a minimally invasive strategy to monitor tobacco's systemic genotoxicity while addressing current diagnostic limitations. Implementation could transform LPK management through earlier intervention and improved OC prevention.

Keywords: Oral leukoplakia, systemic genotoxicity, oral cancer risk prediction, combined biomarker panel

INTRODUCTION:

Oral leukoplakia (LPK) is a red flag a premalignant condition that can evolve into oral cancer (OC) if ignored. LPK, the most common oral potentially malignant disorder, carries a 0.6–20% annual risk of transforming into OC, with tobacco use, particularly smokeless tobacco as its primary driver, systematically damaging DNA and paving the way to disease progression [1]. Decades of research confirm that tobacco, in all its forms, is a leading cause of cancer worldwide. Yet, despite overwhelming evidence, millions continue to use it, unaware of the invisible genetic havoc it wreaks long before cancer manifests.

While tobacco's role in causing localized genetic damage is well-established particularly through buccal cell (BC) micronucleus (MN) cytome (BMNCyt) analysis [2] its systemic genotoxic effects raise critical unanswered

questions. Tobacco-derived carcinogens (e.g., nitrosamines, polycyclic aromatic hydrocarbons) enter systemic circulation, inducing DNA damage in distant tissues. First, how do tobacco carcinogens exert systemic genotoxic effects beyond direct exposure sites? Second, what are the long-term consequences of chronic, low-level DNA damage in distant tissues? Third, how do individual variations in metabolism and DNA repair capacity influence susceptibility to tobacco-induced mutations? Addressing these questions is essential to fully understand the broader implications of tobacco-induced genotoxicity and its contribution to cancer development.

Mechanistic basis of systemic genotoxicity:

Tobacco-derived carcinogens induce systemic genotoxicity through multiple mechanisms, including

direct DNA adduct formation, oxidative stress generation, and chromosomal instability induction. These genotoxic effects are detectable not only in oral epithelium but also in peripheral blood lymphocytes, demonstrating hematogenous routes of tobacco carcinogens and their systemic impact [3]. Biomarkers such as chromosomal aberrations (CAs) [4], cytokinesis-block micronucleus (CBMN) formation [5], and telomerase dysregulation [6] serve as sensitive biomarkers for OC risk assessment, providing a minimally invasive method for early detection. These systemic genotoxicity markers reflect cumulative DNA damage from tobacco carcinogens and correlate strongly with field cancerization effects in the oral epithelium and show significant potential for early risk prediction, yet remain underutilized in current LPK management protocols.

Mechanistic gaps in LPK: Toward integrated biomarkers for OC risk prediction:

LPK poses a significant clinical challenge, with 15–20% of cases progressing to oral squamous cell carcinoma (OSCC). The current diagnostic paradigm for LPK remains limited to clinical-visual examination, and histopathological evaluation. While BMNCyt analysis effectively evaluates localized genotoxicity in LPK, its site-specific nature overlooks systemic biomarkers of carcinogen exposure. This gap is critical, as tobacco and other carcinogens induce distal effects including chronic inflammation, immune evasion, and epigenetic dysregulation that may synergize with local DNA damage to accelerate progression. Despite their potential prognostic value, systemic biomarkers have received inadequate attention in clinical practice, leaving clinicians without reliable tools to identify high-risk LPK patients. To address this, a mechanistic biomarker framework integrating histopathology, localized and systemic genotoxicity is urgently needed. Such an approach would not only clarify LPK's transition to

OSCC but also enable early, targeted interventions for at-risk individuals.

Are we missing vital prognostic information by neglecting systemic genotoxic markers?:

While localized genotoxicity (assessed *via* exfoliated BCs) has been a primary focus in OC risk prediction, significantly less attention has been given to systemic genotoxic damage in blood cells a potential predictor of early cancer risk. Beyond local mucosal effects, tobacco toxins disseminate hematogenously, inducing systemic genotoxicity that mirrors field cancerization. Evidence suggests that CAs, CBMN, and telomerase may serve as promising biomarkers of cancer risk prediction. However, despite their potential, systemic genotoxicity markers remain underutilized in LPK management.

Can integrating systemic genotoxic assessment with conventional diagnostics enhance early OC risk stratification in LPK patients?:

Emerging evidence positions systemic genotoxic markers as potentially transformative tools for LPK risk stratification, addressing three critical limitations of current localized approaches.

1. Circulating biomarkers detects whole-body carcinogen exposure more effectively than site-specific BCs by measuring systemic DNA damage rather than just localized effects
2. Their sensitivity to molecular alterations may detect genotoxic damage before histological changes become apparent, enabling earlier intervention
3. Systemic biomarkers could objectively identify CAs, CBMN formation, and telomerase dysregulation, correlating cancer risk in LPK patients

This three-tiered approach addresses critical blind spots in the LPK management (Figure 1).

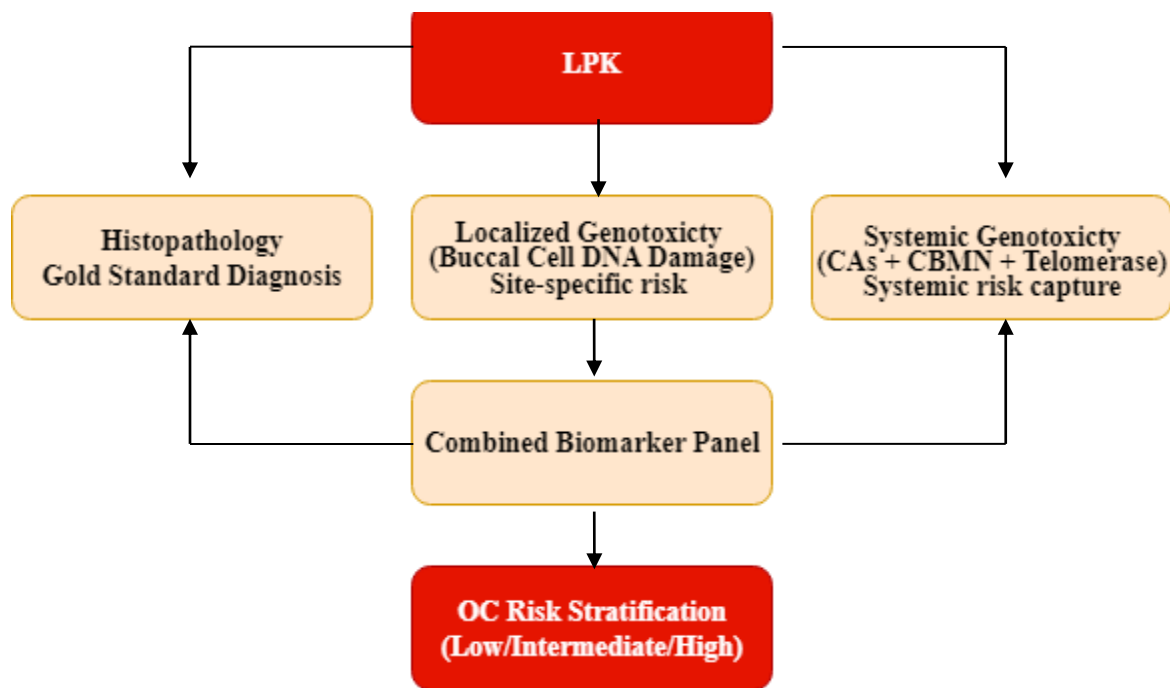


Figure 1: Combined biomarker panel for risk prediction

Histopathology captures localized disease pathology, while systemic genotoxicity biomarkers reflect the patient's total carcinogenic burden and field cancerization effects. The combined use of localized and systemic biomarkers resolves LPK's diagnostic challenges by providing a complete genotoxic profile for accurate risk stratification. Integrating localized and systemic genotoxic markers with conventional histopathology could transform LPK risk stratification by capturing both localized and field carcinogenesis effects.

Future Directions:

The established mechanistic link between systemic genotoxicity and oral carcinogenesis underscores the need to integrate systemic biomarkers (CAs, CBMN, and telomerase) into LPK clinical management. These minimally invasive biomarkers offer three key advantages for precision prevention:

1. Quantification of cumulative tobacco-induced DNA damage across tissues, overcoming the limitations of site-specific assays.
2. Early detection of molecular alterations preceding histological changes, enabling timely intervention.
3. Stratification of high-risk patients (15–20% progression cohort) for targeted surveillance.

Future research should prioritize:

- Prospective validation of biomarkers in LPK cohorts, correlating systemic genotoxicity with malignant transformation rates
- Standardization of protocols for systemic genotoxicity assessment in clinical settings
- Integration with histopathology and localized biomarkers (BMNCyt) to develop a unified risk-prediction model

This paradigm shift toward combined local-systemic biomarker panels could revolutionize early detection and reduce OC mortality through personalized interventions.

CONCLUSION:

Current research supports the use of both local (buccal/tissue) and emerging systemic genotoxicity biomarkers for early detection and risk assessment in oral LPK.

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