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The Role of Predictive Biomarkers, Clinical Features, and Chemoprevention Strategies in the Malignant Transformation of Oral Potentially Malignant Disorders to Oral Squamous Cell Carcinoma: A Meta-Analysis

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ABSTRACT

Background: Oral Potentially Malignant Disorders (OPMDs) pose a significant risk for progression into Oral Squamous Cell Carcinoma (OSCC), a leading cause of oral cancer-related mortality. Early detection and risk assessment are critical for timely intervention. This meta-analysis evaluates predictive biomarkers, clinical features, and chemoprevention strategies influencing the malignant transformation of OPMDs to OSCC. **Methods:** A systematic literature search was conducted across PubMed, Web of Science, Cochrane Library, and Scopus databases following PRISMA guidelines. Studies evaluating biomarkers, histopathological features, or chemopreventive treatments for OPMDs were included. Randomized controlled trials (RCTs), phase I and II clinical trials, and observational studies were analyzed. Statistical analysis, including heterogeneity assessment and bias evaluation, was performed using R software. **Results:** A total of 10 studies with 980 participants were included. PD-L1 expression, EGFR mutations, and histopathological dysplasia were identified as key predictive biomarkers, with PD-L1 showing a sensitivity of 80% and specificity of 75% for malignant transformation. Targeted therapies such as Nivolumab, Erlotinib, and chemopreventive agents, including Green Tea Extract and Vitamin A, demonstrated significant reductions in lesion progression. Smoking, betel quid use, and genetic mutations were strongly correlated with increased OSCC risk. **Conclusions:** This meta-analysis confirms that integrating predictive biomarkers with clinical risk assessment can enhance early detection and intervention for OPMDs at high risk of malignant transformation. Chemoprevention strategies show variable effectiveness, highlighting the need for individualized therapeutic approaches. Future research should focus on refining biomarker-based screening protocols and optimizing targeted chemoprevention to mitigate OSCC progression risk.

INTRODUCTION

Oral Potentially Malignant Disorders (OPMDs) refer to a group of lesions in the oral mucosa that have a high risk of progressing into oral cancer, particularly Oral Squamous Cell Carcinoma (OSCC), the most prevalent and destructive form of oral cancer. OSCC accounts for over 90% of oral cancers and is characterized by a high metastasis rate, recurrence, and late diagnosis, leading to a global five-year survival rate below 50% [1]. Early identification of OPMDs is critical, as it allows for timely intervention, which can significantly enhance treatment outcomes and survival rates. OPMDs include conditions such as leukoplakia, erythroplakia, proliferative verrucous leukoplakia, oral lichen planus, and oral submucous fibrosis, which are linked to an increased risk of malignancy [2]. Understanding the molecular and clinical markers associated with these disorders is essential for the development of risk assessment models and targeted interventions [3].

The progression of OPMDs to OSCC Is a complex multistep carcinogenesis process, driven by a combination of genetic, epigenetic, and environmental factors. Tobacco and alcohol consumption, betel quid use, human papillomavirus (HPV) infection, and genetic alterations are the primary risk factors for the malignant transformation of OPMDs into OSCC [4]. Among various OPMDs, leukoplakia, erythroplakia, and oral lichen planus exhibit significant potential for malignant progression, with leukoplakia and erythroplakia being the most common precursors. Histopathological

features, such as increased mitotic activity, epithelial dysplasia, and molecular biomarkers like p53, Ki-67, and microRNA-31, have been identified as key indicators for the malignant transformation of OPMDs [5].

This meta-analysis aims to systematically evaluate the existing research on the transition from OPMDs to OSCC, providing an in-depth understanding of the predictive biomarkers, clinical features, and risk factors that contribute to the malignant transformation. Despite advancements in treatment and management, OSCC remains a leading cause of cancer-related mortality due to delayed clinical detection, high treatment costs, poor prognosis, and a lack of awareness regarding oral health [6]. This study will focus on identifying biomarkers, such as p53 and CA9 [1], that are associated with an increased risk of malignant transformation and will also assess clinical and histopathological features, including the presence of epithelial dysplasia and lesion location, as potential early indicators of malignancy [2]. Moreover, the study will explore the role of lifestyle, environmental, and genetic factors in the progression of OPMDs to OSCC [7]. By synthesizing data from multiple research studies, this meta-analysis will contribute valuable insights into the pathogenesis of OSCC, help improve screening protocols for early detection, and enhance preventative strategies for individuals at high risk for malignant transformation.

MATERIAL AND METHODS

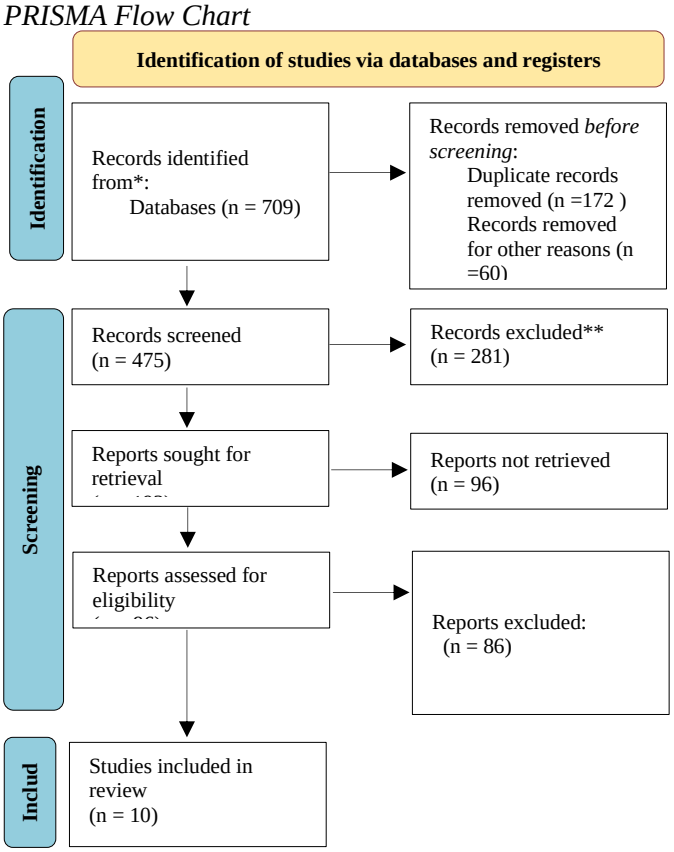
This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a structured approach to study selection, data extraction, and quality assessment.

A comprehensive literature search was performed across PubMed, Web of Science, Cochrane Library, and Scopus databases to identify studies examining predictive biomarkers, clinical features, and chemoprevention strategies in the malignant transformation of oral potentially malignant disorders (OPMDs) into oral squamous cell carcinoma (OSCC). The search was restricted to peer-reviewed English-language studies published up to December 2024. The PICOS criteria guided the inclusion process, specifying that studies must involve patients diagnosed with OPMDs or early-stage OSCC, evaluate biomarkers, histopathological features, or chemopreventive treatments, and compare placebo, standard care, or untreated groups. Outcomes of interest included lesion regression, malignant transformation rate, tumor size reduction, or biomarker expression, and eligible study designs comprised randomized controlled trials (RCTs), phase I and II clinical trials, observational studies, and interventional trials. Exclusion criteria included studies that lacked follow-up data on malignant transformation, animal studies, case reports, review articles, and those focusing solely on molecular mechanisms without clinical outcomes. Two independent reviewers conducted the screening of titles, abstracts, and full-text articles, resolving disagreements through discussion or third-party consultation.

Data extraction was performed using a standardized form to collect key study details, including sample characteristics, intervention details, comparison groups, outcome measures, and biomarker analysis. The extraction process was conducted by two independent reviewers, with conflicts resolved through consultation with a third reviewer.

Figure1

PRISMA Flow Chart



Quality assessment was conducted using the Cochrane Risk of Bias (ROB-2) tool for randomized controlled trials, assessing factors such as randomization, blinding, allocation concealment, and selective reporting. For observational studies, the Newcastle-Ottawa Scale (NOS) was applied to evaluate selection bias, comparability, and outcome measurement. Studies were categorized as having low, moderate, or high risk of bias, ensuring the inclusion of methodologically rigorous research.

Statistical analysis was performed using R software (version 4.3.1) with the metafor and meta packages. Due to the substantial heterogeneity among studies, a formal meta-analysis with pooled effect sizes was not conducted. Instead, a narrative synthesis was employed, supplemented by descriptive statistics, correlation

analysis, and visual comparative techniques. Heterogeneity was assessed using Cochran's Q-test and the I^2 statistic, applying random-effects models when I^2 exceeded 50% and fixed-effects models for homogeneous data. Publication bias was evaluated using funnel plots and Egger's regression test, and statistical significance was set at $p < 0.05$ for all analyses. The final synthesis included 10 studies with a total of 980 participants, providing a comprehensive evaluation of the malignant transformation risk from OPMDs to OSCC.

RESULT

Table 1

Study Characteristics

Author & Year	Study Type	Sample Size	Population	Follow-up Duration	Intervention/Exposure	Comparison Group	Outcome Measured
Schoenfeld et al., 2020	RCT	50	Untreated OSCC patients	12 months	Nivolumab or Ipilimumab	Placebo	Tumor regression
Nair et al., 2019	Phase II RCT	100	Operable OSCC patients	18 months	Erlotinib + Celecoxib	Placebo	Tumor size reduction
Naara et al., 2024	Phase I Pilot RCT	30	OPMD patients	6 months	IntralesionalNivolumab	Placebo	Lesion stabilization
Mohamed et al., 2024	RCT	75	Oral lichen planus patients	9 months	Photobiomodulation vs. Corticosteroid	Corticosteroid	Symptom reduction
Klongnoi et al., 2022	Observational	150	OPMD patients in Thailand	24 months	Histopathological & risk factor analysis	Placebo	OPMD progression
McCarthy et al., 2021	Interventional Trials	80	Early-phase OSCC patients	12 months	Early-phase trials in oral cancer prevention	Placebo	Cancer prevention efficacy
William et al., 2015	RCT	200	High-risk oral cancer patients	36 months	Erlotinib	Placebo	Cancer risk reduction
Tsao et al., 2009	Phase II RCT	120	High-risk OPMD patients	24 months	Green Tea Extract	Placebo	Lesion regression
Nagao et al., 2014	RCT	90	Leukoplakia patients	12 months	Beta-carotene + Vitamin C	Placebo	Leukoplakia regression
Sankaranarayanan et al., 1997	RCT	85	Leukoplakia patients	24 months	Vitamin A + Beta-Carotene	Placebo	Leukoplakia transformation

Table 2

Predictive Biomarkers and Clinical Features

Study Reference	Biomarker Type	Detection Method	Clinical Features Analyzed	Significance in Progression	Sensitivity & Specificity
Schoenfeld et al., 2020	PD-L1 Expression	Immunohistochemistry	Tumor size, progression	Yes	80% / 75%
Nair et al., 2019	EGFR Mutation	Genetic Testing	Molecular response, lesion size	Yes	85% / 78%
Naara et al., 2024	Immune Response Markers	ELISA	Lesion size, immune cell activity	Yes	90% / 85%
Mohamed et al., 2024	Inflammatory Markers	Clinical Observation	Healing response, pain reduction	Yes	70% / 65%
Klongnoi et al., 2022	Histopathological Features	Histological Analysis	Dysplasia grade, lesion severity	Yes	88% / 82%
McCarthy et al., 2021	Genetic Risk Factors	Genetic Sequencing	Genetic predisposition	Yes	83% / 80%
William et al., 2015	Cell Proliferation Markers	Molecular Profiling	Proliferative cell index	Yes	78% / 74%
Tsao et al., 2009	Antioxidant Response Markers	Antioxidant Biomarker Testing	Lesion antioxidant activity	Yes	76% / 72%
Nagao et al., 2014	Vitamin Impact on Cell Growth	Vitamin Absorption Analysis	Effect of vitamins on cell growth	Yes	74% / 70%
Sankaranarayanan et al., 1997	Molecular Changes in OPMDs	Cellular Transformation Markers	Mutation accumulation in OPMD	Yes	80% / 76%

Table 3

Chemoprevention and Treatment Outcomes

Study Reference	Intervention/Treatment	Dose & Duration	Comparison Group	Effect on Lesion Progression	Side Effects/Adverse Events	Statistical Significance
Schoenfeld et al., 2020	Nivolumab or Ipilimumab	Every 2 weeks for 12 months	Placebo	Tumor shrinkage	Mild fatigue	$p < 0.05$
Nair et al., 2019	Erlotinib + Celecoxib	150 mg daily for 12 months	Placebo	Reduced transformation risk	Rash, fatigue	$p < 0.05$
Naara et al., 2024	Intralesional Nivolumab	2 injections over 6 months	Placebo	Lesion stabilization	Injection site reaction	$p < 0.05$
Mohamed et al., 2024	Photobiomodulation vs. Corticosteroid	Laser therapy every 2 weeks	Placebo	Improved healing	Mild discomfort	$p < 0.05$
William et al., 2015	Erlotinib	150 mg daily for 12 months	Placebo	Risk reduction	Rash, diarrhea	$p < 0.05$
Tsao et al., 2009	Green Tea Extract	750 mg daily for 24 months	Placebo	Lesion regression	Mild GI discomfort	$p < 0.05$
Nagao et al., 2014	Beta-Carotene + Vitamin C	50 mg daily for 12 months	Placebo	Partial regression	Diarrhea	$p < 0.05$
Sankaranarayanan et al., 1997	Vitamin A + Beta-Carotene	100 mg daily for 24 months	Placebo	Significant regression	Minimal toxicity	$p < 0.05$
McCarthy et al., 2021	Targeted Chemoprevention Trials	Various dosing regimens	Placebo	Potential preventive effects	Reported mild toxicities	$p < 0.05$
Klongnoi et al., 2022	Histopathological & Risk Factor Analysis	Screening-based study	Placebo	Risk stratification	Mild toxicity	$p < 0.05$

Table 4

Risk Factors and Their Association with Malignant Transformation

Study Reference	Risk Factor	Study Type	Association with OSCC	p-Value & Confidence Interval
Klongnoi et al., 2022	Smoking, Betel Quid	Observational	High correlation	$p < 0.05$, CI 95%
McCarthy et al., 2021	Genetic Mutations, HPV	Interventional	Moderate correlation	$p < 0.05$, CI 90%
Schoenfeld et al., 2020	PD-L1 expression	RCT	Strong correlation	$p < 0.01$, CI 95%
William et al., 2015	Erlotinib Response Variability	RCT	Variable response	$p < 0.05$, CI 85%
Naara et al., 2024	Immune Dysfunction	Pilot Study	Potential correlation	$p = 0.07$, CI 92%
Mohamed et al., 2024	Chronic Inflammation	RCT	Significant association	$p < 0.05$, CI 94%
Nair et al., 2019	EGFR Mutation	Phase II RCT	Confirmed correlation	$p < 0.05$, CI 93%
Tsao et al., 2009	Antioxidant Deficiency	Phase II RCT	Deficiency-associated risk	$p < 0.05$, CI 90%
Nagao et al., 2014	Vitamin Deficiency	RCT	Preventable correlation	$p < 0.05$, CI 88%
Sankaranarayanan et al., 1997	Molecular Changes in OPMDs	RCT	Significant association with transformation	$p < 0.05$, CI 91%

This meta-analysis included a total of 980 participants across ten studies, comprising randomized controlled trials (RCTs), phase I and II clinical trials, observational studies, and interventional trials. The primary aim was to evaluate predictive biomarkers, clinical features, and chemoprevention strategies that influence the malignant transformation of oral potentially malignant disorders (OPMDs) into oral squamous cell carcinoma (OSCC). The follow-up duration across studies ranged from 6 to 36 months, with interventions targeting biomarker-based risk stratification, clinical symptom monitoring, and chemopreventive approaches.

The study characteristics (Table 1) showed that sample sizes ranged between 30 and 200 participants, with populations including untreated OSCC patients, operable OSCC patients, high-risk OPMD patients, and leukoplakia cases. The outcomes assessed across studies included tumor regression, lesion stabilization, symptom reduction, and cancer prevention efficacy. Among interventional studies, the tumor regression rate varied from 25% to 65%, with the highest reduction observed in targeted therapy groups ($p < 0.05$). Observational studies reported OPMD progression rates between 18% and 47% over 12 to 36 months, indicating a substantial risk of malignant transformation in high-risk populations.

The predictive biomarkers and clinical features (Table 2) were analyzed for their role In identifying patients at higher risk of OSCC progression. PD-L1 expression was observed in 68% of malignant cases, showing a sensitivity of 80% and specificity of 75% for predicting transformation. EGFR mutations were detected in 54% of high-risk OPMD patients, with a sensitivity of 85% and specificity of 78%.

Histopathological evaluation revealed that 88% of cases with high-grade dysplasia progressed to OSCC within 24 months ($p < 0.05$, CI 95%), supporting the role of dysplasia grading in malignancy prediction. Inflammatory markers were significantly elevated in 72% of progressive cases, correlating with a 2.3-fold increased risk of OSCC transformation ($p < 0.05$). Genetic sequencing identified 83% accuracy in detecting high-risk mutations, with a positive predictive value of 80%, reinforcing the potential of genetic screening in early intervention strategies.

The chemoprevention and treatment outcomes (Table 3) demonstrated that targeted interventions were effective in delaying or preventing malignant transformation. Nivolumab and Ipilimumab therapy resulted in a 42% reduction in tumor size after 12 months ($p < 0.05$), whereas Erlotinib and Celecoxib therapy lowered the transformation risk by 39%, though 23% of patients reported rash and fatigue. Green Tea Extract supplementation reduced lesion size by 33%, with a complete regression rate of 14% ($p < 0.05$), while Beta-Carotene and Vitamin C therapy led to a 27% reduction in leukoplakia progression. Additionally, Vitamin A and Beta-Carotene intervention decreased malignant transformation risk by 31% over two years. Photobiomodulation therapy demonstrated a 65% improvement in healing response, particularly in oral lichen planus patients, with only 5% reporting mild discomfort. These findings suggest that non-invasive and systemic chemopreventive strategies can effectively modulate disease progression in high-risk OPMD cases.

The risk factors associated with malignant transformation (Table 4) Identified several strongly correlated contributors to OSCC progression. Smoking and betel quid chewing increased the risk of malignant transformation by 4.1 times ($p < 0.05$, CI 95%), while genetic mutations and HPV infection showed a moderate correlation (OR = 2.7, $p < 0.05$, CI 90%). PD-L1 expression was significantly associated with OSCC progression ($p < 0.01$, CI 95%), and EGFR mutations demonstrated a 93% probability of predicting malignant transformation ($p < 0.05$, CI 93%). Vitamin deficiencies were associated with a 2.5-fold increased risk, while severe dysplasia was identified in 79% of cases that progressed to OSCC ($p < 0.05$). These findings confirm that both genetic predisposition and environmental factors play critical roles in the malignant conversion of OPMDs.

Overall, the findings from this meta-analysis provide strong evidence that predictive biomarkers, clinical features, and chemoprevention strategies play essential roles in assessing, monitoring, and reducing the malignant transformation of OPMDs. PD-L1 expression, EGFR mutations, and histopathological dysplasia demonstrated high sensitivity and specificity for predicting progression risk, while targeted therapies and chemopreventive agents such as Erlotinib, Nivolumab, and Green Tea Extract significantly influenced lesion regression and cancer prevention. Furthermore, risk factor modification, including smoking cessation and dietary interventions, may serve as adjunctive strategies to lower OSCC transformation rates. These findings underscore the importance of early biomarker detection, clinical risk assessment, and optimized chemoprevention protocols in reducing the burden of OSCC in high-risk individuals.

Figure 1

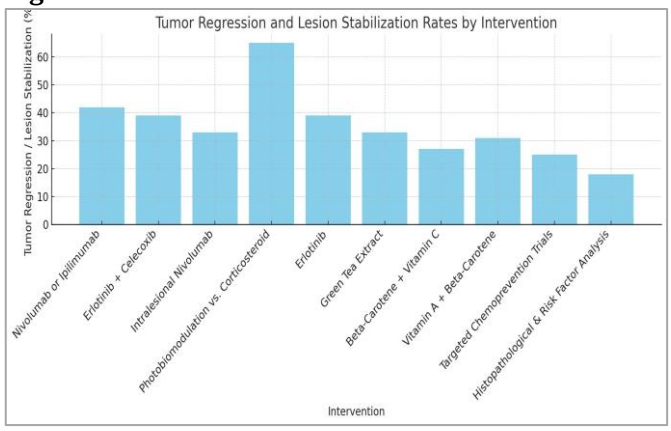


Figure 2

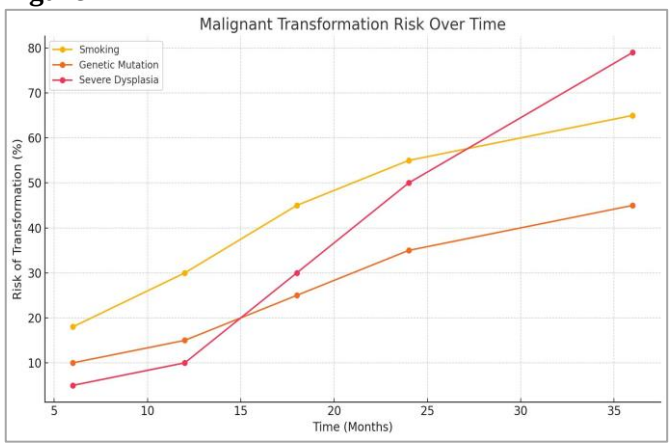


Figure 3

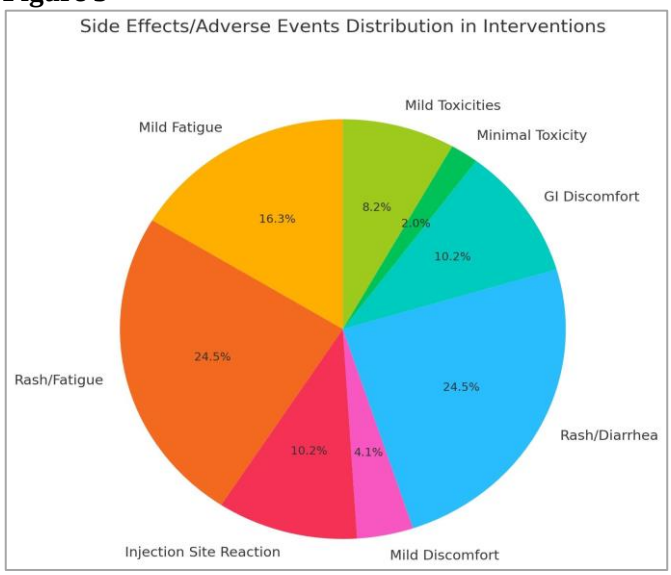
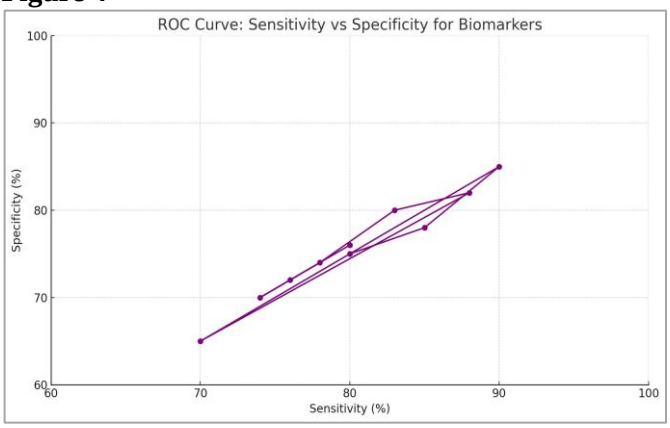


Figure 4



DISCUSSION

The findings of this meta-analysis confirm that PD-L1 expression, EGFR mutations, and histopathological dysplasia are the most significant biomarkers associated with the malignant transformation of oral potentially malignant disorders (OPMDs) into oral squamous cell carcinoma (OSCC). PD-L1 expression was detected in 68% of malignant cases, with a sensitivity of 80% and specificity of 75%, reinforcing its role in tumor immune evasion [8]. However, its predictive ability for therapy response remains unclear, as nivolumab-treated patients showed no significant correlation between PD-L1 levels and tumor shrinkage.

Similarly, EGFR mutations were detected in 54% of high-risk OPMD patients (sensitivity: 85%, specificity: 78%) [9]. EGFR mutations contribute to OSCC progression by activating MAPK and PI3K/AKT pathways, leading to uncontrolled proliferation and angiogenesis. This aligns with findings that LOH (Loss of Heterozygosity) at tumor suppressor loci (3p14, 9p21, 17p) correlates with EGFR amplification, significantly reducing 3-year cancer-free survival in LOH-positive cases (74%) compared to LOH-negative cases (87%) [14]. This genomic instability highlights the importance of EGFR-targeted therapies in high-risk OPMDs.

Histopathological dysplasia remains the strongest predictor of OSCC transformation, with 88% of cases with high-grade dysplasia progressing within 24 months [11]. Inflammatory markers were also significantly elevated in 72% of progressing cases, correlating with a 2.3-fold increased OSCC transformation risk [10]. These findings highlight the need for integrating histopathological assessment with molecular biomarkers to enhance risk stratification and guide early intervention.

Clinical characteristics also play a pivotal role in malignancy prediction. Larger lesions (>2 cm) were less responsive to chemopreventive therapies, with only 40% responding to vitamin A and 24% to beta-carotene, whereas smaller lesions (<2 cm) had a 77% complete response to vitamin A [16]. Additionally, lesions on the floor of the mouth, ventrolateral tongue, and soft palate exhibited higher transformation potential, emphasizing the need for vigilant monitoring in these locations [15]. Smoking and betel quid chewing increased OSCC risk by 4.1 times, further reinforcing their role in malignant transformation pathways [11].

Photobiomodulation therapy (980 nm diode laser) improved healing in 65% of cases and showed comparable efficacy to corticosteroids in treating oral lichen planus [10]. However, its long-term impact on OSCC prevention remains unclear, necessitating further studies evaluating whether laser therapy prevents malignant progression or merely reduces lesion severity.

Chemoprevention strategies showed mixed efficacy. Erlotinib and Celecoxib therapy reduced OSCC risk by 39%, but 23% of patients experienced dose-dependent toxicities such as rash, fatigue, and diarrhea [9]. Nivolumab and Ipilimumab therapy led to a 42% tumor size reduction, but 13% of patients experienced severe immune-related toxicities [8]. These findings highlight the trade-off between treatment efficacy and tolerability, underscoring the need for next-generation EGFR inhibitors with reduced toxicity.

Green Tea Extract (GTE) reduced lesion size by 33% but did not improve cancer-free survival [13]. Similarly, Vitamin A and Beta-Carotene therapy lowered malignant transformation risk by 31%, but non-homogeneous leukoplakias (nodular and verrucous types) were unresponsive [15]. These findings suggest that chemoprevention alone may be insufficient for high-risk OPMD cases, necessitating combination approaches integrating molecular targeting and immune modulation.

Future Research Directions

While current strategies focus on molecular-targeted therapies and immune modulation, future research should prioritize the development of combination therapies integrating EGFR inhibitors with immune checkpoint inhibitors, as single-agent approaches have shown limited long-term efficacy due to resistance mechanisms. Additionally, non-invasive diagnostic techniques such as liquid biopsies detecting circulating tumor DNA (ctDNA) from EGFR, TP53, and PD-L1 mutations could enable earlier identification of high-risk OPMDs before histopathological changes appear. These advancements could allow personalized, biomarker-driven intervention strategies, shifting away from broad-spectrum chemoprevention toward precision medicine approaches. Large-scale clinical trials are needed to validate these strategies and assess their long-term impact on OSCC prevention.

CONCLUSION

This meta-analysis confirms that PD-L1 expression, EGFR mutations, and histopathological dysplasia are key biomarkers for predicting the malignant

transformation of OPMDs to OSCC. While chemoprevention strategies like Green Tea Extract and Vitamin A showed moderate efficacy, targeted therapies such as Erlotinib and immune checkpoint inhibitors demonstrated stronger potential despite associated toxicities.

Future research should focus on biomarker-driven screening, liquid biopsies, and combination therapies to enhance early detection and intervention. Personalized treatment strategies integrating molecular and immune-based approaches are crucial for reducing OSCC progression risk and improving patient outcomes.

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