Received: 15 May 2024 | Revised: 9 July 2024 | Accepted: 17 July 2024

DOI: 10.1111/jop.13573

REVIEW

Journal of Oral Pathology & Medicine WILEY

Diseases with oral malignant potential: Need for change to inform research, policy, and practice

Antonio Celentano | Nicola Cirillo

Melbourne Dental School, Faculty of Medicine, Dentistry & Health Sciences, University of Melbourne, Parkville, Victoria, Australia

Correspondence
Nicola Cirillo, Melbourne Dental School, Faculty of Medicine, Dentistry & Health Sciences, University of Melbourne, Parkville 3010, Victoria, Australia.
Email: nicola.cirillo@unimelb.edu.au

Abstract

This manuscript critically examines the current classification of oral potentially malignant disorders, questioning the practicality and implications of labeling such a large population as precancerous, given that the actual progression to oral cancer is significantly low for most disorders. The paper advocates for a revised classification system that accurately reflects the varying malignancy risks associated with different disorders. It suggests a reassessment of the diagnostic and management approaches to mitigate overdiagnosis and alleviate patient burdens. We propose categorizing diseases with oral malignant potential as follows: *Oral Precancerous Diseases*, encompassing high-risk lesions and conditions like erythroplakia, non-homogeneous leukoplakia, proliferative leukoplakia, and actinic keratosis; *Oral Potentially Premalignant Diseases*, covering lesions, conditions, and systemic diseases with distinct oral manifestations harboring a limited or undefined risk of transformation, such as homogeneous leukoplakia, oral submucous fibrosis, oral lichenoid diseases, chronic hyperplastic candidosis, keratosis of known aetiology (smokeless tobacco, khat), palatal lesions in reverse smokers, and dyskeratosis congenita; and *Systemic Conditions with Oral Malignant Potential* including Fanconi's anemia, xeroderma pigmentosum, and chronic immunosuppression (including patients post-bone marrow transplantation), which are associated with an increased risk of oral cancer without preceding precursor lesions. We provide illustrative examples to demonstrate how this framework offers practical guidance for research, policy-making, and clinical practice.

KEYWORDS
OPMD, oral cancer, precancerous conditions, precursor lesions

1 | INTRODUCTION: THE NEED FOR A REVISED APPROACH

The goal of early cancer detection is to diminish cancer-related morbidity and mortality, with the identification of precancerous lesions seen as a pivotal strategy in achieving this objective.[1] Take, for instance, potentially malignant disorders of the oral cavity (OPMDs), which are linked to an increased risk of oral cancer development; thus, pinpointing these precursor lesions has long been recognized as a crucial step towards early cancer detection.[2] However, despite these efforts, global mortality rates for oral cancers have remained stagnant in the last 30 years,[3] a disappointing and concerning trend sharply contrasting with the declining rates observed for other cancer types.[4] Epidemiological evidence underscores wide disparities in oral cancer incidence and survival across socio-demographic and geographical variables, likely influenced by differences in healthcare accessibility

and patterns of risk factor exposure. This underscores the imperative for policy reforms and a more innovative, evidence-driven approach to addressing the global burden of oral cancer.

Recently, we questioned the need to consider many of these conditions as potentially malignant in the first place.[5] Globally, close to half a billion individuals are afflicted by oral diseases that are earmarked as potential precursors to cancer. The designation of such a substantial portion of the population as abnormal and requiring intervention raises significant concerns, especially given that only a minute fraction may derive actual benefits. It is probable that the majority of patients harboring "precursor" lesions are not on a trajectory towards cancer development, rendering the diagnosis of OPMD potentially more deleterious than advantageous. The detriments associated with the anxiety stemming from a pre-cancer diagnosis, the necessity for rigorous follow-ups, and the prospect of invasive treatments can assume notable proportions when extended to a broad demographic. Recent research suggests that the diagnosis and subsequent management of OPMD can engender substantial out-of-pocket expenditures, precipitating catastrophic health-related financial burdens for households.[6,7] Furthermore, the psychological toll exacted on these patients, manifesting as depression, anxiety, and stress, is noteworthy,[8] prompting the formulation of strategies aimed at enhancing patient–provider communication.[9]

Hence, the decision to apprise a patient of the potential progression of their OPMD to cancer warrants careful consideration, mindful of its wider ramifications. In this article, we introduce a refined classification designed to provide a framework for assessing the constrains of the existing paradigm and advocating enhancements to this framework.

2 | CRITERIA FOR INCLUSION IN THE OPMD GROUP

An OPMD is defined as "any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer."[2] However, the precise criteria (and supporting literature) for inclusion remain somewhat ambiguous. With the exception of the most prevalent disorders, data regarding the malignant progression of other OPMDs are sparse, making it technically infeasible to demonstrate a "statistically increased risk" of transformation. Notably, the roster of OPMDs enumerated in the latest WHO Classification of Head and Neck Tumours[10] differs from that presented in consensus documents[2] (Table 1).

There exists primarily anecdotal evidence regarding the malignant transformation of oral lupus erythematosus, with most documented cases involving carcinomas on the lips.[13] Consequently, uncertainty persists regarding whether the risk solely pertains to the lip vermilion rather than the intraoral structures.[10] Conversely, actinic cheilitis/keratosis demonstrates a relatively well-established malignant transformation rate (14%),[12] yet it has been earmarked for removal in the latest WHO classification,[18] presumably due to its extraneous location outside the oral cavity and distinct pathogenesis. Similarly, while a considerable body of evidence suggests the potential premalignancy of chronic hyperplastic candidosis,[19] this condition has been omitted. A recent systematic review on "candidal leukoplakia" revealed varying malignant transformation ratios of 2.5%, 6.5%, and 28.7%.[20] The WHO Collaborating Centre's working group concluded that "such a wide range implies inconsistent diagnostic criteria",[2] hence deeming insufficient epidemiological evidence for its malignant potential. However, disparate rates of malignant transformation are also observed for other OPMDs, raising questions as to why this rationale for exclusion was selectively applied to chronic hyperplastic candidosis.

Significant inconsistencies also manifest in systemic diseases presenting as, or with, OPMDs. This encompasses oral GVHD, where extensive chronic GVHD significantly escalates the risk of developing all solid tumors,[14] as does the transplant procedure itself (especially hematopoietic), owing to pre- and long-term treatments.[21] However, specific evidence indicating a distinct increased risk associated with oral lesions in GVHD (typically exhibiting a lichenoid appearance) remains inconclusive.[14,22]

In the latest classification of OPMDs,[18] inherited cancer syndromes,[17,23] including dyskeratosis congenita, have been expanded to incorporate Fanconi anemia, xeroderma pigmentosum, Li-Fraumeni syndrome, Bloom's syndrome, ataxia-telangiectasia, and Cowden syndrome. Nonetheless, the statistically heightened risk of developing oral cancer for all these rare familial syndromes is yet to be firmly established,

TABLE 1 List of oral potentially malignant disorders for which there is either an unclear risk of transformation or inconsistencies in the classification.

Disease	Risk [Ref.]	WHO list 2022	Consensus report 2020
Erythroleukoplakia	10.7 per 1000[11]	Yes	No[a]
Actinic keratosis/cheilitis	14%[12]	No	Yes
Lupus erythematosus	RR 1.92–3.98[13]	Yes	Yes
(Oral) graft versus host disease	RR 1.4–2.9[14]	Yes	Yes
Smokeless tobacco keratosis	Undefined[15]	Yes	No
Palatal lesions in reverse smokers	Undefined[16]	Yes	Yes
Familial cancer syndromes	Varies (mostly undefined)[17]	Yes	Yes[b]

[a]The consensus of the current Working Group was to classify erythroleukoplakia under non-homogeneous leukoplakia.
[b]Only dyskeratosis congenita is listed among the precursor oral lesions.

with supporting evidence lacking for some. For instance, up-to-date, no reports demonstrate a direct association between oral squamous cell carcinoma (OSCC) and Li-Fraumeni syndrome,[24] with most other associations being anecdotal. Furthermore, it remains unclear why these syndromes, despite lacking clinically visible precursor lesions, are included in the OPMD list. Consider Fanconi anemia, a genetic disorder characterized by genomic instability associated with various cancers: only a small minority of these patients exhibit an OPMD (with a prevalence akin to the general population), while most develop OSCC de novo.[25]

Lastly, individuals with other systemic diseases such as chronic fatigue syndrome and post-bone marrow transplantation (BMT) patients are also at an increased risk of OSCC.[26] Hence, the criteria for including or excluding certain conditions from the list of OPMDs remain ambiguous, as exemplified by the case of epidermolysis bullosa, a mucocutaneous disease sporadically associated with malignancy,[27] being omitted from the latest OPMD list.

In conclusion, the evidence supporting the inclusion or exclusion of certain conditions from the OPMD lacks clarity, as does the methodology and consensus-building process (e.g., the utilization of guidelines for reporting consensus-based methods and the approach to reaching consensus). Without greater consistency in these aspects, one could argue for the consideration of other diseases that clinically present as ulcers and are sporadically linked to malignancy, such as aphthous stomatitis and trauma. Notably, a retrospective analysis of real-world data from approximately 150 000 patients has revealed a significantly elevated risk of developing OSCC in individuals with recurrent aphthous stomatitis.[28] Moreover, chronic mucosal injuries have been associated with an increased relative risk (RR) of OSCC in a large retrospective study.[29] While the list of conditions is expanding to encompass entities like somatoform disorders and bruxism,[30] none of these has been suggested for inclusion in the OPMD group. Therefore, excluding diseases with weak or uncertain associations from the OPMD list would be a prudent decision.

3 | OPMDS VERSUS PRECANCEROUS LESIONS AND CONDITIONS

The World Health Organization (WHO) initially introduced the term "oral potentially malignant disorders" in 2007,[31] a designation recently reaffirmed in a consensus report from the WHO Collaborating Centre for Oral Cancer.[2]

The choice of the term "disorder" is significant as it conveys the concept of mucosal field change, signaling an elevated risk of developing OSCC, either at the same site as the original OPMD or elsewhere in the oral cavity. The deliberate selection of "potentially malignant" over "premalignant" is noteworthy. Whereas "premalignant" suggests an inevitable progression to OSCC, diagnosing OPMD indicates an increased statistical risk of evolving into OSCC, without certainty. OPMD is crafted to encompass both precursor "lesions," such as a clinical white patch, and specific precursor "conditions," like oral submucous fibrosis.

The term "condition" better elucidates the concept of field cancerization, describing a broad area or "field" of tissue that has undergone precancerous changes, extending beyond a single tumor or lesion. Field cancerization, as originally referenced,[32] is not unique to oral cancer and is also recognized in various malignancies of the gastrointestinal (GI) tract.[33] While evidence of field cancerization exists in clinically normal oral mucosa,[34] evidence for field defects in OPMDs is limited.[35] Currently, it appears to be more of a working hypothesis than an established fact. Thus, it is reasonable to postulate that OSCC may develop from field abnormalities in "conditions" like submucous fibrosis and proliferative verrucous leukoplakia (PVL), while transformation in localized lesions such as oral leukoplakia is likely to be site-specific.

This distinction carries significant clinical implications, extending far beyond mere academic discourse; for instance, intervention may be more feasible or effective for localized lesions than for conditions. Supporting this perspective, a recent systematic review found no current treatments reduce the recurrence of PVL.[36] Although some evidence suggests interventions on OPMDs may not decrease malignant transformation compared to surveillance,[37,38] larger lesions (>200 mm^2) pose a higher risk of transformation[39] and could warrant removal. Emerging evidence indicates excision might reduce the recurrence rates in high-grade oral mucosal epithelial dysplasia,[40] and laser surgery shows promises in treating oral leukoplakia.[41,42]

The challenge in obtaining conclusive evidence for the efficacy of interventions that reduce cancer risk may stem from the classification of OPMDs and the risk stratification of individual disorders. For example, removal might effectively address localized leukoplakia in the absence of field changes, yet this effect could be obscured by a more heterogeneous sample in studies. Additionally, reliance on index incisional biopsies for diagnosis, which may not accurately represent the lesion's status, complicates data interpretation. Complete surgical removal offers an ethically acceptable means to investigate the extent of unknown dysplasia or malignancy at other sites in these lesions, which in turn has the potential to improve our understanding of the disease process. Therefore, distinguishing between lesions and conditions, and persisting in the use of the term "premalignant," remains valuable, providing a practical framework for research, policy, and clinical practice.

4 | PROPOSAL FOR A NEW CLASSIFICATION

We propose the following classification for oral diseases with malignant potential:

4.1 | Oral precancerous diseases (OPD, lesions and conditions)

This category encompasses high-risk "clinical variants of leukoplakia",[43] such as erythroplakia, leuko-erythroplakia (non-homogeneous

leukoplakia, which carries a significantly higher risk of transformation compared to the homogeneous type[44]), and proliferative leukoplakia, as recently described[45]; oral diseases presenting with dysplasia; and actinic keratosis/cheilitis. OPD are distinguished by a higher rate of transformation and the presence of dysplasia at initial biopsy. With an estimated cumulative transformation rate of ~10% or higher, and an annual transformation rate >1%, the term "premalignant" here reflects the substantial likelihood of malignant transformation, indicating the need for strict surveillance and/or treatment where feasible. It is plausible that, given enough time, these diseases will invariably progress to cancer. Early oral cancer often presents as erythroplakia, hence some OPDs could indeed be incident OSCC that have not yet been diagnosed as such. These are the diseases that general dentists need to be trained to recognize effectively.

4.2 | Oral potentially premalignant diseases (OPPD)

This category encompasses lesions, conditions, and systemic diseases with well-defined oral manifestations, such as homogeneous leukoplakia, oral submucous fibrosis, smokeless tobacco keratosis, oral lichenoid diseases (oral lichen planus, oral lichenoid lesions, and reactions, and oral GVHD), chronic hyperplastic candidosis, and dyskeratosis congenita (most patients present with oral white patches[46]). We also include lesions associated with regional risk factors, such as keratosis in khat chewers and palatal lesions in reverse smokers, and primarily lip lesions associated with Discoid Lupus Erythematosus (DLE). These diseases have a lower (cumulative transformation rate ≤10%, or <1% annually) or undefined/unclear risk of transformation, or may be reversible after cessation of the causative stimulus, making them suitable for monitoring and the removal of risk factors where possible. The large majority of patients in this category will not develop cancer during their lifetime and hence should not be overdiagnosed as having a precancerous disease. Management should be focused on avoidance of behavioral risk factors and symptomatic care.

4.3 | Systemic conditions with oral malignant potential

These are systemic diseases with an increased risk of oral cancer, even in the absence of specific oral precursor lesions. Examples include Fanconi's anemia, xeroderma pigmentosum, and immunosuppressed patients, including those post-BMT and affected by Systemic Lupus Erythematosus (SLE) (where cumulative immunosuppressant exposure is the likely cause of the observed increase in cancer risk). Management of these conditions generally falls outside the realm of dental practice, though patients may be referred to a dentist for overall monitoring. It is noteworthy that these patients are susceptible to a range of blood and solid tumors, not just oral cancer; indeed, some of the syndromes listed by the WHO as OPMDs have not been directly linked to oral cancer (see Section 2). In our view, these should be regarded as predisposing factors rather than potentially malignant diseases.

5 | FURTHER IMPLICATIONS FOR RESEARCH, POLICY AND PRACTICE

A notable feature of the proposed classification is its reinstatement of the distinction between lesions and conditions, aiming to facilitate the development of clinical procedures. For instance, from a surgical standpoint, recommending excision and follow-up for premalignant *lesions* (when clinically appropriate and with acceptable morbidity) versus follow-up and periodic rebiopsy for potentially malignant *conditions* seems reasonable. However, if surgical excision fails to reduce subsequent cancer incidence and mortality, such interventions should be regarded as overtreatment, defined as excessive, unnecessary, or too frequent treatment for a condition that would never cause symptoms or death,[47] or one that would not prevent death due to the disease. To mitigate overtreatment, it is crucial to prevent overdiagnosis initially, and the risk-stratification approach of this classification provides a framework to achieve this aim.

From a public health and policy perspective, this classification aims at reducing overdiagnosis and preventing harm to patients while optimizing resources for oral cancer surveillance and detection. It offers a framework for policymakers but should not be viewed as prescriptive. As discussed earlier, the epidemiology of oral cancer varies geographically, thus local practices should reflect these differences. For instance, in Asia, oral submucous fibrosis may be considered a high-risk condition for public health purposes due to its high prevalence in regions where oral cancer incidence and mortality are rising, shared risk factors with oral cancer, and distinct clinical and pathological features that reduce the likelihood of misdiagnosis (compared to, e.g., leukoplakia vs other benign keratoses). Policymakers, rather than academics, should make such policy choices. Still, from an evidence-based standpoint, it would be incorrect to categorize submucous fibrosis in the high-risk group because: 1. the actual risk of transformation is around 4% over many years, hence the annual malignant transformation rate is relatively small; 2. there is no effective treatment to reduce the risk of transformation, aside from ceasing chewing habits; 3. the condition is prevalent in Southeast Asia and the Pacific, and labeling it as precancerous would potentially turn tens of millions of individuals into *may-be* cancer patients unnecessarily.

From a clinical and educational perspective, the classification provided in this article aims to simplify and streamline the detection of early cancer by emphasizing only the most crucial pathologies—precancerous lesions and conditions. This approach reduces the complexity and breadth of clinical manifestations of precancerous diseases that require immediate action. Many GDPs overlook the assessment and diagnosis of oral cancer and may not be well trained in identifying early precursor lesions.[48] Recognized obstacles to performing routine oral examinations by GDPs include their limited knowledge and experience.[49] In agreement with this view, research suggests that general

dentists often lack confidence and perform inadequately in addressing suspicious lesions.[50,51] A recent study from Japan indicated that misdiagnosis of malignant lesions by family dentists was a significant risk factor for referral delays from family dentists to core hospitals/specialists.[52] Additionally, insufficient skills, knowledge, and confidence among GDPs in detecting mouth cancer and precursor lesions may lead to inadequate preventive education for patients,[53] which is extremely important as oral cancer is typically linked to lifestyle factors and hence largely preventable. This revised approach is vital to optimize the training of GDPs on premalignancy since only a minority of oral cancers are preceded by precancerous lesions. Typically, early-stage lesions do not manifest as distinct OPMDs, although they most often appear as red,[54] as well as white or mixed red-white lesions (which may overlap with the clinical manifestation of precancerous lesions). Leveraging on the clinical manifestations of oral (pre)malignancies rather than widening the breadth and scope of OPMDs would allow providing more impactful clinical education.

Historically, the differentiation between lesions and conditions (which was once used) has never been proven molecularly, partly because the high throughput and -omics era has coincided with a shift in approach and nomenclature leading to the broader definition of OPMDs. From a research perspective, therefore, our classification provides an opportunity for reconciling the epidemiology and molecular biology of precursor lesions and to extend the pilot work on field cancerization to understand if it is a hallmark of precancerous conditions, and whether it is implied in the recurrence of OSCC. Another puzzling aspect that could be investigated with the lens of this revised approach is that surgical removal of leukoplakias does not lead to better outcomes in terms of cancer development.[37] This could be due to the data distortion generated when considering leukoplakias as one entity—which now belong to two different categories, namely OPD and OPPD—as well as from key missing information regarding the role of the microenvironment and/or field changes—which our classification now highlights as a key feature by differentiating lesions from conditions. Finally, the differing epidemiology of OPD (relatively rare but with a high transformation rate) and OPPD (common but with a low transformation rate) highlights the need for the development of distinct biomarkers and risk prediction tools for oral precursor lesions.[55]

6 | CONCLUSIONS

In conclusion, our manuscript advocates for a paradigm shift in the classification and management of OPMDs. By reevaluating the inclusion criteria and distinguishing between precancerous lesions and conditions, we propose a refined framework that emphasizes evidence-based risk assessment and tailored interventions. This approach aims to mitigate overdiagnosis, reduce overtreatment, and optimize resources for oral cancer surveillance and detection globally. We invite the clinical and research community to embrace this proposal with courage, leaving behind chronic non-supported positions, and to collaborate in advancing a more effective, patient-centered approach to early cancer detection. Our paper advocates for the establishment of a new expert working group tasked with developing a robust deliberation process for implementing this revised classification system. This group should prioritize evidence-based epidemiological datasets and inclusive methods for expert membership, ensuring a comprehensive and effective approach to advance the still neglected field of oral oncology.

ACKNOWLEDGMENT

Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/jop.13573.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Antonio Celentano https://orcid.org/0000-0003-4293-2511
Nicola Cirillo https://orcid.org/0000-0003-1429-1323

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How to cite this article: Celentano A, Cirillo N. Diseases with oral malignant potential: Need for change to inform research, policy, and practice. *J Oral Pathol Med*. 2024;53(8):495-501. doi:10.1111/jop.13573