doi: 10.1111/j.1600-0714.2007.00582.x

J Oral Pathol Med (2007) 36: 575–80

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REVIEW ARTICLE

Nomenclature and classification of potentially malignant disorders of the oral mucosa

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At a workshop coordinated by the WHO Collaborating Centre for Oral Cancer and Precancer in the UK issues related to terminology, definitions and classification of oral precancer were discussed by an expert group. The consensus views of the Working Group are presented here. The term, 'potentially malignant disorders', was recommended to refer to precancer as it conveys that not all disorders described under this term may transform into cancer. Critically evaluating all definitions proposed so far for oral leukoplakia, the Working Group agreed that the term leukoplakia should be used to recognize 'white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer'. An outline was proposed for diagnosing oral leukoplakia that will prevent other oral white disorders being misclassified as leukoplakia. The Working Group discussed the caveats involved in the current use of terminology and classification of oral potentially malignant disorders, deficiencies of these complex systems, and how they have evolved over the past several decades. The terminology presented in this report reflects our best understanding of multi-step carcinogenesis in the oral mucosa, and aspires to engender consistency in use.

J Oral Pathol Med (2007) **36:** 575–80

Keywords: leukoplakia; potentially malignant disorders; precancer, oral; WHO Collaborating Centre

Introduction

An international working group comprising specialists in the fields of epidemiology, oral medicine and pathology and molecular biology with a special interest in oral cancer and precancer met in London in May 2005 to discuss current concepts, the terminology, classifications, the natural history, pathology and of molecular markers and to critically analyse the evolution of knowledge and practice concerning the diagnosis and management of what have been traditionally called, collectively, precancerous lesions and conditions of the oral mucosa. The workshop was coordinated by the WHO Collaborating Centre for Oral Cancer and Precancer in the UK. A series of discussion papers on the above aspects were prepared in advance by experts, discussed extensively at the Workshop and subsequently revised. A series of reports are to be issued, of which this is the first: it focuses on nomenclature, definitions and classifications with some clear recommendations from the Working Group designed to reflect our advancing understanding of the biology of oral precancer, and to achieve consistency in diagnosis in clinical practice. Consensus views of the working group are shown in italics where any change in the terminology or definitions is recommended.

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Accepted for publication April 2, 2007

Concept of precancer

The concept of denoting some lesions or disorders of the oral mucosa as 'precancerous' is based on the evidence that:

1. In longitudinal studies, areas of tissue with certain alterations in clinical appearances identified at the first assessment as 'precancerous' have undergone malignant change during follow-up.
2. Some of these alterations, particularly red and white patches, are seen to co-exist at the margins of overt oral squamous cell carcinomas.
3. A proportion of these may share morphological and cytological changes observed in epithelial malignancies, but without frank invasion.
4. Some of the chromosomal, genomic and molecular alterations found in clearly invasive oral cancers are detected in these presumptive 'precancer' or 'premalignant' phase[s]..

The terms 'pre-cancer', 'precursor lesions', 'premalignant', 'intra epithelial neoplasia' and 'potentially

malignant' have been used in the international literature to broadly describe clinical presentations that may have a potential to become cancer. They all convey the concept of a two-step or multi-step process of cancer development, but it is unlikely, on *a priori* grounds, that there is uniformity in the way individual patients or tissues behave. The terminology ought to reflect our best understanding of carcinogenesis in the oral mucosa, and aspires to engender consistency in use. The latest WHO monograph on Head and Neck Tumours (2005) uses the term 'epithelial precursor lesions' (1).

The consensus of the present working group was to recommend the term 'potentially malignant disorders', as it conveys that not all lesions and conditions described under this term may transform to cancer, rather that there is a family of morphological alterations amongst which some may have an increased potential for malignant transformation. Potentially malignant disorders of the oral mucosa are also indicators of risk of likely future malignancies elsewhere in (clinically normal appearing) oral mucosa and not only site-specific predictors.

A much earlier working group of the World Health Organisation proposed in 1978 that clinical presentations of the oral cavity that are recognized as precancerous (hereafter referred to as potentially malignant disorders – see above) be classified into two broad groups, as lesions and conditions (2), with the following definitions:

- a precancerous lesion is 'a morphologically altered tissue in which oral cancer is more likely to occur than in its apparently normal counterpart';
- a precancerous condition is 'a generalized state associated with a significantly increased risk of cancer'.

This took account of worldwide experience that 'oral precancer' has clinically diverse appearances. A range of precancerous lesions and conditions was recognized in that report. These are listed in Table 1. The distinction between a precancerous lesion and a precancerous condition was considered not just academic. At the time these terms were coined, it was considered that the origin of a malignancy in the mouth of a patient known to have a precancerous lesion would correspond with the site of precancer. On the other hand, in precancerous conditions, cancer may arise in any anatomical site of the mouth or pharynx. It is now known that even the clinically 'normal' appearing mucosa in a patient harbouring a precancerous lesion may have dysplasia on the contralateral anatomic site (3) or molecular aberrations in other oral mucosal sites suggestive of a pathway to malignant transformation, and that cancer could subsequently arise in apparently normal tissue (4). The current Working Group, therefore, did not favour subdividing precancer to lesions and conditions and the consensus view was to refer to all clinical presentations that carry a risk of cancer under the term '*potentially malignant disorders*' to reflect their widespread anatomical distribution.

Table 1 Classification of precancerous lesions and conditions [WHO (5)]

Precancerous lesions	*Precancerous conditions*
Leukoplakia	Submucous fibrosis
Erythroplakia	Actinic keratosis
Palatal lesions in reverse smokers	Lichen planus
	Discoid lupus erythematosus

Terminology and definitions of potentially malignant disorders

Leukoplakia

The WHO Collaborating Centre for Oral Precancerous Lesions in 1978 sought to define 'oral leukoplakia' sufficiently tightly to provide an internationally accepted system to characterize 'white patches' that carry an increased risk of malignant potential (5). Over a 25 year period the WHO definition for leukoplakia has been quoted by researchers and clinicians alike, and adapted or refined by other working groups and experts at several international seminars. International attempts to define/refine the WHO definition of oral leukoplakia are shown in Table 2 (1, 5–8).

The question should be asked whether the WHO (1978, 1997) definitions have outlived their purpose (5, 8). A definition for a specific disorder is needed to facilitate exchange of information among epidemiologists, clinicians and pathologists to assist in the evaluation of results of interventions, to compare treatment outcomes and, at times, to indicate prognosis. Rather than broadly grouping all white patches – the majority of which are harmless – under one umbrella,

Table 2 Defintions of oral leukoplakia proposed in the past decades

Working group	*Definition*
WHO (5)	A white patch or plaque that cannot be characterized clinically or pathologically as any other disease
First International Conference on oral leukoplakia. Malmo, Sweden (6)	A white patch or plaque that cannot be characterized clinically or pathologically as any other disease and is not associated with any physical or chemical causative agent except use of tobacco
International Symposium, Uppsala, Sweden (7)	A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable disease
WHO (8)	A predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion
WHO (1)	Not defined – no distinction is made from other white patches
Warnakulasuriya *et al.* (this report)	Leukoplakia should be used to recognize white plagues of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer

the WHO definitions allow a system of grouping together those that carry an increased risk of malignant transformation. This is to some extent achieved, largely by exclusion of those white patches with no recognized link to cancer.

Having considered all proposed definitions the working group agreed to amend the original 1978 WHO definition to stand as: '*The term leukoplakia should be used to recognize white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer*'. Furthermore leukoplakia is a clinical term and the lesion has no specific histology. It may show atrophy or hyperplasia (acanthosis) and may or may not demonstrate epithelial dysplasia. It has a variable behavioural pattern but with an assessable tendency to malignant transformation. It must be noted that oral epithelial dysplasia has no specific clinical appearance and the term should not be used as a clinical descriptor of a white lesion.

Clinical types

Two main clinical types of leukoplakia are recognized, being *homogeneous* and *non-homogeneous* leukoplakia. The distinction of these is purely clinical, based on surface colour and morphological (thickness) characteristics, and do have some bearing on the outcome or prognosis. Homogeneous lesions are uniformly flat, thin and exhibit shallow cracks of the surface keratin. The risk of malignant transformation is relatively low. Non-homogeneous lesions carry a much higher risk of malignant transformation;

Non homogeneous varieties include:

- speckled: mixed, white and red, but retaining predominantly white character;
- nodular: small polypoid outgrowths, rounded red or white excrescences;
- verrucous: wrinkled or corrugated surface appearance.

The consensus view of the working group was that broadly dividing leukoplakia to homogeneous or non-homogeneous categories was imprecise and of limited value. However, those with mixed white and red plaques should be recognized as having a higher risk status. These are to be denoted as 'erythroleukoplakia'.

- proliferative verrucous leukoplakia (PVL) presents with multiple, simultaneous leukoplakias (9); as the disease is visibly multifocal and frequently covers a wide area. This clearly fits with the proposed terminology of 'potentially malignant disorder' rather than struggling to list PVL under 'lesions' or as a 'condition'.

Additional clinical descriptions that may assist in the characterization of oral leukoplakia are recommended. These are:

A Aetiological description: clearly associated with tobacco or areca nut use; idiopathic.
B Site description giving anatomical sub-site in the mouth or oropharynx (ICD-DA/ICD-10).
C Size or extent of the lesion(s).

A provisional diagnosis of leukoplakia is made when a predominantly white lesion at clinical examination cannot be clearly diagnosed as any other disease or disorder of the oral mucosa (Table 3). A biopsy is mandatory. A definitive diagnosis is made when any aetiological cause other than tobacco/areca nut use has been excluded and histopathology has not confirmed any other specific disorder.

Table 3 Disorders that need exclusion to diagnose leukoplakia

Disorder	*Diagnostic features*	*Biopsy*
White sponge nevus	Noted in early life, family history, large areas involved, genital mucosa may be affected	Biopsy not indicated
Frictional keratosis	History of trauma, mostly along the occlusal plane, an etiological cause apparent, mostly reversible on removing the cause	Biopsy if persistent after elimination of cause particularly in a tobacco user
Morsicatio buccarum	Habitual cheek – lip biting known, irregular whitish flakes with jagged out line	Biopsy not indicated
Chemical injury	Known history, site of lesion corresponds to chemical injury, painful, resolves rapidly	Not indicated
Acute pseudomembranous candidosis	The membrane can be scraped off leaving an erythematous/raw surface	Swab for culture
Leukoedema	Bilateral on buccal mucosa, could be made to disappear on stretching (retracting), racial	Not indicated
Lichen planus (plaque type)	Other forms of lichen planus (reticular) found in association	Biopsy consistent with lichen planus
Lichenoid reaction	Drug history, e.g. close to an amalgam restoration	Biopsy consistent with lichen planus or lichenoid reaction
Discoid lupus erythematosus	Circumscribed lesion with central erythema, white lines radiating	Biopsy consistent with DLE supported by immunofloresence and other investigations
Skin graft	Known history	Not indicated
Hairy leukoplakia	Bilateral tongue keratosis	Specific histopathology with koilocytosis; EBV demonstrable on ISH
Leukokeratosis nicotina palate	Smoking history, greyish white palate	Not indicated

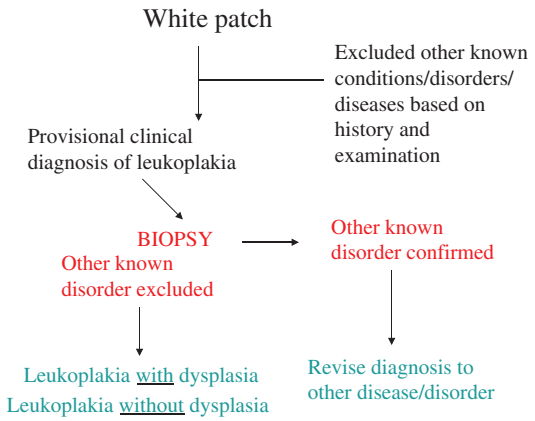

Figure 1 Schematic representation of the steps in diagnosis of oral leukoplakia.

A schematic diagram to assist recognition of oral leukoplakia by eliminating other mucosal disorders was drawn up by experts at the workshop and is presented in Fig. 1.

Following biopsy, if no other disorder is confirmed, the lesion is further characterized as leukoplakia with or without dysplasia. In spite of numerous suggested prognostic molecular markers (10), the presence of epithelial dysplasia as assessed by light microscopic examination is still the strongest predictor of future malignant transformation in an oral potential malignant disorder (11, 12). The role of histopathology, its positive and negative predictive values, and hence its value and limitations – or utility – in predicting malignant transformation are discussed in a future publication from this series.

A staging system for oral leukoplakia combining clinical aspects and pathology findings has been proposed (13), while in Table 4 a proposal for the reporting of treatment results of leukoplakia is presented (14). It should be noted that these suggestions have not been validated yet.

Table 4 Reporting of treatment results of oral leukoplakia: a proposal [modified from Miller et al. (11)]

Type of treatment
Surgical (incl. CO_2)
Non-surgical
Chemo-prevention
Observation only
Response rate (in case of non-surgical treatment or observation without treatment)
No response (stable disease)
Partial response (> 50% reduction in size, but not complete)
Complete response
Progressive disease (> 25% increase in size or the appearance of a new lesion)
Recurrence
Leukoplakia at the same subsite, irrespective of time interval
New primary
Leukoplakia at a distinctly different subsite
Malignant transformation
Malignant event in the head-and-neck region, outside the oral cavity
Malignant event outside the head-and-neck region
Length of follow-up

Table 5 Differential diagnosis of erythroplakia

Nature of condition	*Diagnostic category*
Inflammatory/immune disorders	Desquamative gingivitis
	Erythematous lichen planus
	Discoid lupus erythematosus
	Pemphigoids
	Hypersensitvity reactions
	Reiter's disease
Infections	Erythematous candidiasis
	Histoplasmosis
Hamartomas/neoplasms	Haemangioma
	Kaposi's sarcoma

Adapted from Reichart and Philipsen (15).

Erythroplakia

Oral erythroplakia has long been considered the oral mucosal 'lesion' with the greatest potential for malignant transformation in the mouth. The definition has not changed very much over a period, and the 1978 WHO definition is still current and widely used (6): 'A fiery red patch that cannot be characterized clinically or pathologically as any other definable disease'. The present working group endorsed this definition as it is used worldwide to distinguish this red lesion. It must be noted that erythroplakia is often flat with a smooth or granular surface. Numerous other red patches/macules that could arise on the oral mucosa should be excluded before considering erythroplakia as the diagnosis (15). These are listed in Table 5. Erythroplakias seem to be relatively uncommon on their own and often present as mixed red-and-white lesions. These should be considered under the term 'erythroleukoplakia' as explained earlier.

Palatal lesions in reverse smokers

This disorder is specific to populations who smoke with the lighted end of the cigar, cigarette or cheroot inside the mouth, resulting in red, white or mixed lesions of the palate. There are no difficulties in defining/diagnosing this lesion once this particular habit among an individual/community is noted. All changes related to this habit are noted on the palate (16).

Oral submucous fibrosis

Oral submucous fibrosis (OSF) is a chronic disorder characterized by fibrosis of the lining mucosa of the upper digestive tract involving the oral cavity, oropharynx and frequently the upper third of the oesophagus. Except in early forms of the disease the clinical presentation is characteristic due to fibrosis of lamina propria and submucosa with an increasing loss of tissue mobility. Different populations may show different sites of involvement within the mouth. The early and late forms of presentation are outlined in Table 6. OSF is well recognized as a potentially malignant disorder (17, 18).

Actinic keratosis

Actinic keratosis is considered to represent a potentially malignant condition of the lip (8). The squamous

Table 6 Clinical presentations of oral submucous fibrosis

Early forms	*Late presentation*
Burning sensation, excerbated by spicy food	Fibrous bands within mucosa
Vesiculation	Limitation of mouth opening
Blanching of mucosa	Narrowing of oropharyngeal orifice with distortion of uvula
Leathery mucosa	Woody changes to mucosa and tongue

epithelium of the lip vermilion may be hyperplastic or atrophic and shows disordered maturation, varying degrees of keratinization, cytological atypia and increased mitotic activity on microscopic examination. The underlying connective tissue usually shows basophilic degeneration of collagen and elastosis (8). A provisional diagnosis may be made on clinical grounds, but definitive diagnosis requires biopsy.

Lichen planus
Lichen planus is a chronic inflammatory disorder demonstrating some immune pathology. It is a cell-mediated immune condition of unknown aetiology, in which T lymphocytes accumulate beneath the epithelium of the oral mucosa and increase the rate of differentiation of stratified squamous epithelium, resulting in hyperkeratosis and erythema with or without ulceration (19). There is considerable controversy as to the potentially malignant nature of this condition (20), while some opinion leaders have stated that lichen planus carries an unequivocal malignant potential and an unspecified risk (21). Lichen planus and lichenoid lesions have characteristic, but not pathognomic, clinical and histological appearances, usually allowing distinction from oral leukoplakia: the plaque type of lichen planus may, however, often resemble leukoplakia, emphasizing the importance of biopsy in diagnosis.

There are difficulties in distinguishing lichen planus from lichenoid lesions or lichenoid contact lesions (22).

Discoid lupus erythematosus
Discoid lupus erythematosus (DLE) is a chronic autoimmune disease of unknown aetiology. Clinical distinction of DLE from lichen planus and erythoplakia could sometimes be difficult. There are conflicting data from the literature as whether to regard oral DLE as a potentially malignant disorder. Malignant transformation is reported when DLE affects the lip than intra oral sites.

Hereditary disorders with increased risk
Two conditions that may have an increased risk of malignancy in the mouth are dyskeratosis congenita (DC) and epidermolysis bullosa. They are rare hereditary conditions, most cases of DC are X-linked and affect males. Patients with DC often develop white plaques on the dorsal tongue which may be confused with leukoplakia, but the absence of habits and their young age may point to the hereditary nature of this disorder (23). Malignant change within the areas of white patches is reported.

Conclusions

The terminology and classifications proposed at this workshop strengthen the understanding of what is already known and continues terms and systems which have shown their value in epidemiological field and clinical studies. It is unreal to change widely used classifications that have helped us satisfactorily in monitoring diseases and evaluation of studies but it is important that we explain the caveats involved in their use and any deficiencies of these complex systems, and understand how they have evolved over the past several decades. We have sought to tighten the definition of oral leukoplakia. Use of the schematic outline proposed for diagnosing leukoplakia will prevent other oral white disorders being misclassified as leukoplakia. We will not succeed in recommending that certain terms in universal use be summarily abandoned, but must lead in educating how these terms should be used within the framework of international consensus.

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