**Risk factors and aetiopathogenesis of Potentially Premalignant Oral Epithelial Lesions**

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Abstract

Potentially malignant oral mucosal disease has some ability to give rise to malignancy of the oral epithelium i.e. oral squamous cell carcinoma (OSCC). The present article provides a succinct review of the possible or probable causes of potentially premalignant oral epithelial lesions (PPOEL). There is a focus upon studies that examined the causes or aetiological associations with clinically likely or histopathologically detectable oral epithelial dysplasia.

## Introduction

Potentially malignant oral mucosal disease has some ability to give rise to malignancy of the oral epithelium i.e. oral squamous cell carcinoma (OSCC). As noted however in the accompanying articles there has been, and indeed remains, inconsistency with the terminology or definitions of such disease, hence in turn there is inevitably the risk that describing or defining the causes and evolution of such disease is challenging and at times evidence is contradictory and/or misleading. The present article aims to provide a succinct review of the possible or probable causes of disease (effectively oral epithelial dysplasia) that has some potential to give rise to OSCC. Detailed discussion of oral carcinogenesis is out with the scope of this article, although suitable recent reviews can be found elsewhere.

Oral carcinogenesis is typified by a series of sometimes reversible molecular and cellular events that culminate in neoplasia and thus it would be expected that some of the known causative factors of potentially malignant oral diseas will be similar to those of OSCC. There is substantial evidence that the life style factors including tobacco, alcohol and betel nut (and related products) use, and probably sexually acquired Human Papilloma Virus (HPV) will cause the vast majority of instances of OSCC, hence it is not surprising that Potentially Premalignant Oral Epithelial Lesions (PPOELs) may be similarly caused by, or associated with, these factors – other than (at present) – infection by HPV. Table 1 provides a summary of the factors that may drive oral epithelial dysplasia. This article will now consider each of these in more detail.

## Likely common risk factors of potentially malignant oral mucosal disease

### *Tobacco products*

An association between tobacco use and oral cancer has long been established. Several systematic reviews have strongly supported the association between

distinctive forms of tobacco exposure (both smoked and smokeless) with an increased risk of OSCC [1-10]. Although oral leukoplakia is the most common PPOEL, its association with tobacco use has not been evaluated as greatly as that of OSCC. In addition, changes in the definition and nomenclature of PPOEL cause interpretation of results of previous studies to be challenging [11].

Although the association between tobacco consumption and oral leukoplakia has long been described [12-14], genuine evidence-based causal link is still missing [11]. Nevertheless non-prospective observational studies have pointed to an association between smoking and oral leukoplakia [15]. Similarly, simple logic would suggest that a disease process that ultimately causes oral cancer will have similar aetiological factors as OSCC. A large population-based Taiwanese study showed that high-risk individuals, namely cigarette smokers and betel cheweers, present a 2,7 relative risk of developing oral leukoplakia or oral cancer and screening them seems to be an effective approach to reduce oral cancer-related mortality [16]. In fact, Taiwanese individuals with oral cancer seems to smoke 469 packs of cigarette per year, for 28.5 years, together with 12,508 betel quid pieces per year, for 23.3 years, before presenting oral cancer [17]. A retrospective study of 15,811 US individuals demonstrated that risk factors for oral leukoplakia included male gender, current cigarette or pipe/cigar use, smokeless-tobacco use, ever alcohol consumption and diabetes mellitus. The number of cigarettes smoked per day was closely associated with a risk of oral leukoplakia. A Hungarian cross-sectional study performed during an oral screening program found that 3.7% of the individuals presented with PPOEL and among these, 88% reported tobacco use [18]. In individuals residing in rural US, smokeless tobacco was strongly associated with the presence of oral leukoplakia [19]. Individuals with tobacco-related lesions have an increased risk of oral epithelial dysplasia [20]. Tobacco positively influences the risk of PPOEL (particularly leukoplakia) and the presence of mucosal lesions that, predictably, include nicotinic

stomatitis [21, 22] - yet this latter disorder does not commonly transform to malignancy. A recent meta-analysis has indicated that the malignant transformation of PPOEL is influenced by the clinical appearance (e.g. non-homogenous leukoplakia is more likely to transform than homogeneous) and location (the lateral border of the tongue is a site of particular concern) [23].

In addition, smoking cessation seems to produce beneficial results to populations by reducing oral leukoplakia prevalence and oral cancer incidence, thus leading to a time-dependent benefit to former smokers [24]. More importantly, stop smoking in or before middle age avoid most of the eventual risk of developing cancer of the oral cavity and after 10 year of smoking cessation oral cancer risk seems to be similar to a never smoker [24, 25]. This approach also may reverse the presence of oral leukoplakias [26] and even reduce the prevalence of these PPOEL [27].

There is considerable literature on the etiological mechanisms by which smokeless tobacco can cause cellular changes that may result in PPOEL. These will not be reviewed in detail in this article but smokeless tobacco products contain several carcinogens, with nitrosamines being the most significant and they can be used by chewing and snuff [28]. Among them, 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) and N0-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol(NNAL) are the most prevalent tobacco specific nitrosamines (TSNAs) with high carcinogenic potency linked to several tumors [29, 30]. NNN was demonstrated to be abundant in oral fluids of smokers and non-smokers and associated with esophageal and oral cancers, being the NNN/cotinine ratio increased in second hand smoke [30].

The use of smokeless tobacco products has increased considerably across the globe, probably as a consequence of escalation in the cost of cigarettes and the incorrect belief that smokeless tobacco is less harmful to the mouth than smoked tobacco. Although smokeless tobacco has long been associated with oral cancer risk, there is still a misconception of its “harmless nature” associated with the

reduced tobacco-related disease risks [31]. Nevertheless, significant variation in its composition, with varying amount of several carcinogens, associated with long-term TSNAs exposure limits the interpretation of epidemiology studies [32]. Certainly, oral leukoplakia can precede OSCC in snuff users [28], and a recent meta-analysis of studies derived from Southern Asia demonstrated that smokeless tobacco is a risk for all PPOEL (OR=20.0, 95% CI=12.3-32.5), although the risk for oral leukoplakia is not as substantial (OR=4.33, 95% CI 1.4-13.2) [33]. Shammah, a traditional form of snuff dipping tobacco, is a significant risk factor of oral leukoplakia, indeed in persons in Yemen current Shammah use is significantly associated with the presence of PPOEL (OR= 12.99; 95% CI: 6.34-26.59). A study of US professional baseball players demonstrated that a reduction in the frequency of oral leukoplakia may be linked to a fall in consumption of smokeless tobacco over a 10-year period [34]. Aside from PPOEL, smokeless tobacco may impact overall oral health, increasing the rates of tooth loss, edentulousness, and gingival recession [35]. Unsurprisingly clinically detectable oral mucosal changes are common in tobacco chewers – for example arising in nearly half from a sample of low-income Indian adults [36]. Some lesions such as oral lichen planus are unlikely, however, despite being potentially malignant, to be caused by smokeless (or indeed smoked) tobacco. A cohort study reported that a six week cessation of smokeless tobacco habit in young males caused resolution of almost all instances of leukoplakia [37]. This does, however, seem a rather remarkable finding that warrants further investigation. Cessation of tobacco use is clearly beneficial to many aspects of oral health, although there is a need for further supportive studies [38].

*Alcohol products*

Alcohol is a risk factor for many cancers, including those of the head and neck. The type of alcoholic beverage and the frequency of consumption can influence any cancer risk, and risk is increased with concomitant tobacco use [39, 40]. Oral cancer

risk seems to be related to overall alcohol consumption (drink-years) and not drinks/day [41]. Although there is a strong positive association between alcohol and OSCC risk, the evidence of such an interaction between alcohol and PPOEL is less strong or less evident.

Protein adducts with aldehydic end products are expressed in oral leukoplakia and OSCC [42], and an association between alcohol consumption and oral leukoplakia was found in a large cross-sectional study. A case-control study in India found that alcohol drinking was a significant risk factor for oral leukoplakia - even among non-users of tobacco or other related products, this being particularly so in females [43]. A previous cross-sectional study reported that 7+ alcoholic drinks per week was associated with oral epithelial dysplasia (OR=2.4) after controlling for confounders such as tobacco use [44]. In 2007, the same group interviewed patients with oral epithelial dysplasia and OSCC and observed that smoking was similarly associated with both conditions but drinking was more strongly associated with oral cancer [45]. A large prospective cohort study reported that alcohol use was an independent risk factor for PPOEL; alcohol drinkers had a higher risk than non-drinkers for both PPOEL and oral dysplasia and the association with tobacco had a more-than-additive (i.e. not synergistic) effect upon PPOEL risk [46]. At the present time, while there remains a need for appropriately designed long-term prospective studies, alcohol should be considered an etiological risk factor for PPOEL.

*Oral submucous fibrosis*

Oral submucous fibrosis (OSMF) is caused by exposure to a host of agents, particularly arecoline in areca nut. Present evidence suggests a 3.72% or greater malignant transformation rate for OSF [47],[48] with the rate of occurrence of leukoplakia within OSMF being about 24% and being a predictor of later OSCC. The

mechanisms that underlie the malignant potential of OMSF are well reviewed elsewhere but include genetic and epigenetic events that culminate in OSCC [47].

Oncogenic Human Papilloa Virus (HPV) subtypes – potential risk factor

Human papilloma virus (HPV) is now recognized as a cause of OSCC. It would thus be expected that such an association also exists with respect to PPOEL. The oncogenic types, particularly 16 and 18, are, like the cervical, penile and peri-anal mucosae, the most likely causes of oral mucosal carcinogenesis [49]. Oral acquisition of HPV is positively associated with sexual behaviour [50, 51]. Nevertheless, the association with OSCC only really applies to disease of the posterior of the tongue, tonsils and upper pharynx [52],[53]. There can be a raised prevalence of HPV DNA and p16 prevalence in OSCC (in general) than in the normal oral epithelium, but it seems to be lower than in oropharyngeal carcinomas [54, 55]. The use of different techniques to viral detection, the lack of data on site of origin of samples and unclear information on risk factors exposures limits present understanding of HPV role in OSCC, but evidence does support the belief that HPV is a risk factor for some, but not all, OSCC [54-56].

It might thus be expected that there is a demonstrable association between oncogenic types of HPV and PPOEL [52, 57], but available data are presently not perhaps as consistent as those of some OSCCs. The detection rate of HPV in oral leukoplakia varies greatly according to the methods of analyses [58]. Rates of HPV DNA detection have been 17.6% in oral leukoplakia and 19.7% in oral lichen planus (OLP) - much higher rates than healthy oral mucosa (5.6%) [59]. Others have reported similar results for HPV DNA in both oral leukoplakia (22.2%) and OLP (15.4%), with oncogenic types (16 and 18) being the most commonly identified subtypes [59]. Sikka *et al* [60] found HPV DNA in more than 40% of oral leukoplakia

lesions but its presence was not associated with any particular grade of dysplasia. Detection using p16 immunoexpression have similarly yield variations in HPV presence in PPOEL [61]. It might have been expected that a strong link between HPV and cause of PPEOL would be reflected in a higher rate of HPV (particularly oncogenic types) in erythroplakia than leukoplakia but HPV infection rates in the former (although not evaluated to any notable extent) seem to be of similar rates as those of the latter [62].

An early meta-analysis of case reports and case series showed that HPV is three times more likely to be detected in PPOEL and 4.7 times more likely to be identified in OSCC than in normal mucosa [63]. A more recent meta-analysis reported that HPV oncogenic types have a higher prevalence in PPOEL than in healthy epithelium; this association applied to both cellular or tissue samples and thus supports the notion of a strong association between HPV and PPOEL [54]. Nevertheless, prospective studies are necessary to evaluate whether the presence of HPV may predict malignant progression of PPOEL [54, 64]. Furthermore there remains concerns that any association between oncogenic types of HPV and oral leukoplakia (or oral epithelial dysplasia) may not have considered the site of the leukoplakia (which is bound to be of relevance) [65] and the social background of affected individuals. It may be, and indeed probable, based upon the patterns of HPV-associated OSCC, that virally driven PPOEL is a distinct group [65] in which affected individuals may have exposures to alcohol, tobacco and HPV that are different to patients of the past and hence have disease driven more by HPV than by tobacco and/or alcohol – and affecting the posterior aspects of the tongue and mouth.

Oncogenic and non-oncogenic types of HPV have been detected in oral lichen planus (OLP), and indeed a systemic review suggested an association between HPV and OLP [54]. There is insufficient evidence to state that either HPV acquisition or

carriage is associated with particular clinical or histopathological types of OLP or that the presence of oncogenic types of HPV influence any malignant potential of OLP. Finally, there is no consistent pattern of carriage of particular HPV types (oncogenic or non-oncogenic) across the globe. Thus, at the present time, while oncogenic types of HPV can be within the mouths or lesions of patients with OLP, it remains unclear if such an association is of relevance to the aetiopathogenesis and malignant potential of OLP. Human papilloma virus, including oncogenic types, has been detected in oral submucous fibrosis. There are, however, few relevant studies [52] and thus at the present time it cannot be concluded that HPV is a cause of any premalignant potential of oral submucous fibrosis.

Uncommon risk factors

*Candidal infection*

It has long been proposed that candidal infection may be a cause of oral epithelial dysplasia, although there remains no definitive supportive evidence. Since the 1980's it has been suggested that the production of nitrosamines by Candida species may influence the malignant transformation of PPOEL and oral cancer risk [66]. However while the presence of *Candida* may be associated with PPOEL and OSCC risk [67] there are remarkably few truly convincing data that this fungal infection drives oral carcinogenesis. A retrospective study reported Candidal infection to be associated with dysplasia and tongue lesions and suggested that antifungal treatment should be considered in these cases [68] – but there is no convincing evidence that this has a long term clinical benefit – and may thus be medico-legally concerning. A cross-sectional study observed that nearly half of the oral leukoplakias cases were infected with Candida spp, mostly *C. albicans,* with tobacco smoking, betel-quid chewing and alcohol consumption being strongly associated with the presence of candidal infection [69]. Betel-quid chewing was also associated with candida infection in a

study with female Cambodians [70]. Patients with OSMF can have an elevated level of candidal infection and the number of colony forming units (CFUs) may increase with the increased duration of betel-quid chewing habit [71]. Patients with OLP also have higher rates of candidal infection rate than healthy individuals and may have a shift to a species other than *C. albicans* [72].

Patients with Chronic Mucocutaneous Candidiasis, particularly those with Autommune Polyendocrinopathy Candidal Ectodermal Dystrophy (APECED) may be at risk of OSCC and oesophageal malignancy [73],[74]. This may reflect the generation of carcinogenic agents by specific candida strains or perhaps altered immune surveillance, but it is independent of tobacco and/or alcohol exposure. Thus, in highly rare instances it may be possible for candida species to give rise to oral epithelial dysplasia or neoplasia. Nevertheless, despite evidence that candidal carriage may be more frequent or of higher load in patients with PPOEL than others, that some candidal species can generate carcinogenic agents, and that candidal infection can be associated with oral epithelial dysplasia or OSCC, there remains no substantial or consistent proof that this infection is a common cause or driver of the evolution and malignant transformation of PPOEL.

*Treponema pallidum* infection

Syphilis, the infection of *Treponema pallidum*, has long been proposed as a risk factor of OSCC, however there are few data to support this notion and there are very few reports of the precise histopathology of “syphilitic leukoplakia” that confirm that this is a truly potentially malignant lesion. An epidemiological study of 16,420 people diagnosed with syphilis and resident in the US (1972-87) did however find an elevated standardized incidence ration for cancers of the oral cavity – and particularly the tongue. However, it remains unclear whether any risk of OSCC (and

PPOEL) in syphilis is a direct consequence of infection, it's treatment or the result of recognized causative factors for oral malignancy [75].

*Oral lichen planus*

Oral lichen planus (OLP) is considered to be a potentially malignant disorder although a lack of clear diagnostic criteria and conflicting reports on malignant transformation have hampered understanding of the precise likelihood of OLP transforming to OSCC [76-78]. Only a small subset of OLP lesions would seem to transform to malignancy, but the OSCCs may be multiple and may not always be at sites of existing OLP [79]. A systematic review of 16 observational studies of 7,086 patients with OLP suggested an average rate of malignant transformation of 1.09% with an annual transformation rate ranging from 0.36 to 0.69%. The tongue was the most common location in which malignant transformation occurred [80]. A later meta-analysis of 57 studies that included 19,676 patients reported a malignant transformation rate of 1.1% with tobacco smoking, alcohol use, and HCV infection being possible risk factors for malignant transformation [81].

The exact mechanism by which OLP induces OSCC is not known, and indeed there would seem to be few, if any, studies that demonstrate that OLP transforms to OSCC via histopathologically or clinically proven PPOEL. Certainly there are molecular parallels with other chronic inflammatory disorders (that are known to cause malignancy – for example ulcerative colitis, Barrett's oesophagitis and others) [82],[83]. Image-based DNA ploidy (i.e. indicating gross DNA changes) can be abnormal in some OLP lesions and may predict later malignant transformation of some, but not all, lesions. Aldehyde dehydrogenase status may increase the risk of OSCC (adjusted odds ratio of 6.71) in patients with OLP [84]. Moreover, expression

of Bmi1, a stem cell marker, may be associated with an elevated risk of malignant transformation of OLP [85].

Thus, at the present time, OLP seems to have some potential to drive the development of OSCC in a minority of patients. However, the risk factors for such change are largely unknown – and do not presently include HPV. If the malignant potential of OLP was caused by inflammation driven genetic and/or epigenetic change it might be expected that lupus-like disease would increase the risk of OSCC and indeed OED – and indeed there are some, all be it limited, data to support this notion [86]. Similarly as lichenoid lesions of Graft versus Host Disease (GvHD) may have some malignant potential it is probable that some types of long standing inflammation within the oral mucosa may drive the evolution of PPOEL and later epithelial malignancy [87, 88]. An inflammation-driven process might also explain the rare instances of OSCC (and presumably prior OED) in hereditary epidermolysis bullosa.

*Systemic sclerosis (scleroderma)*

Patients with scleroderma (systemic sclerosis) are at risk of a variety of malignancies and there is some evidence that this may include a risk of OSCC [89]. A meta-analysis of observational studies showed a standardized incidence ratio for overall incidence of cancer as 1.41 [90]. A nationwide study in Taiwan [91] reported a cancer incidence of 6.9 per 1000 person-years in 2053 individuals with scleroderma and notably the oral cavity and pharynx were the second most prevalent sites (n=11), after the lungs (n=21). A prospective study of 769 US-based patients with scleroderma, representing 3775 patient-years found 9 instances of tongue OSCC. The standardized ratio for tongue OSCC was 25 times higher than that expected in an age-adjusted population from an official US cancer registry [92]. In another study, the same group reported 90 cases of cancer among this same cohort of SSc

individuals, pointing to an overall increase in the incidence of cancer with a marked increase in the rate of oesophagal and oropharyngeal malignancies [93].

It has been speculated that the carcinogenic potential of scleroderma may be associated with chronic inflammation, disease-related immunosuppression or disease treatment [94]. It could of course reflect an increased permeability to carcinogens via the atrophic epithelium, or immunodeficiency-related HPV infection (hence explaining the tongue or pharyngeal tumours)

*Genetic disease*

As might be expected, disorders cause dysregulation of DNA metabolism of the oral epithelium may give rise to PPOEL and/or OSCC. Dyskeratosis congenita (Zinsser-Engman-Cole syndrome) is a rare genetically determined disorder associated with abnormal telomere length [95]. It is clinically characterized by cutaneous hyperpigmentation, nail dystrophy, oral leukoplakia and progressive bone marrow failure [96]. White patches, usually referred to in the relevant literature as leukoplakias, develop in childhood and are eventually present in over 80% of patients [97, 98]. The exact histopathology of these white patches has rarely been described, although of note they may initially have no features of OED, but patients (both children and adults) have a high risk of OSCC – 1000 times greater than non-affected individuals [95].

Bloom syndrome (BS; congenital telangiectatic erythema) is a rare autosomal recessive disorder of DNA helicase function and characterized by sun sensitivity, telangiectatic erythema of the face, and stunted growth [99]. Up to 20% of the patients with BS develop cancer across their lifetime, and the most common cancers include lymphomas, leukaemia, oral/oesophagal squamous cell carcinoma as well as adenocarcinoma of the colon [100, 101].

Fanconi anemia (FA) is characterized by a mutation in one of 20 involved genes leading to chromosomal instability and defects in DNA repair [102]-[103, 104]. Fanconi anemia gives rise to progressive bone marrow failure, skeletal and cutaneous anomalies and a significantly increased risk of malignancies, particularly head and neck squamous cell carcinoma [103, 105]. A study of patients from the German Fanconi Anemia Registry observed a 50-fold increase in total cancer risk with a 650-fold increase in head and neck cancer risk among FA patients [106]. Presumably the OSCC does not manifest de-novo, but is preceded by PPOEL. Of note, however, oral leukoplakias have been observed in up to 12% of children with Fanconi anaemia prior to hematopoietic stem cell transplantation (HSCT) [107]. Such therapy does not however, remove the risk of later PPOEL (including proliferative verrucous leukoplakia) or OSCC.

Xeroderma pigmentosum, rare autosomal recessive disorder of nucleotide excision repair, increases the risk of carcinomas on sun-exposed skin (and hence the lips). There have been rare instances of gingival and tongue OSCC [88, 108] and presumably such genetic abnormalities first causes histopathologically evident OED), suggesting that perhaps factors other than sunlight may drive malignancy in this genetic disorder. Actinic cheilitis is a risk factor for SCC (and OED) of the lips [109] but there is no evidence that this UV light driven malignant potential truly applies to intr-oral epithelial surfaces).

*Haematinic and micronutrient deficiency*

Haematinic deficiency (e.g. iron, folate or vitamin B12) can cause histopathological and/or clinically detectable PPOEL presumably by interfering in epithelial proliferation [110]. Plummer Vinson syndrome (characterized by dysphagia, iron deficiency and oesophalgeal webbing) can give rise to post-cricoid or oesophageal SCC) although

there is no substantial evidence of an increased risk of OED or OSCC. In addition such gross deficiency states are unlikely to be a common cause of PPOEL and deficiencies of micronutrients are probably of minor importance in the development of PPOEL [111].

**Summary and Conclusions**

The causes or risk factors of PPOEL in general parallel those of OSCC. There is relatively good evidence that tobacco and/or alcohol are drivers of OED, and it would be expected, provided appropriate research is undertaken, that oncogenic types of HPV will be of etiological importance to the development of some PPOEL. Instances of PPOEL so occasionally arise as a direct consequence of candidal infection, chronic inflammation (e.g. OLP) or dietary (or other causes of) insufficiency of haematinics, and of course genetically determined disease that interferes in DNA metabolism.

For now, to improve both understanding of the long-term consequences of PPOEL, there is a need to settle upon whether research should be focused upon disease defined at a molecular (e.g. genetic/genetic), cellular, tissue or clinical level. Certainly to continue to base research upon clinically detectable “leukoplakia” is not justified – as the vast majority of these lesions do not represent at least histopathologically decetable cellular atypia or epithelial dysplasia. To date, knowledge has derived from research of clinically determined PPOEL and as a consequence the literature remains at times confusing and conflicting – and thus ultimately delays the development and instigation of appropriate treatment and prevention strategies.

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